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Medical case reports: Some theoretical and empirical perspectives

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LIST OF ABBREVIATIONS

AIDS:	Acquired Immune Deficiency Syndrome
BPS:	Biopsychosocial
CARE:	CAsE REport (guidelines)
CR:	Used to denote either Case Report, Case Series, or Case Reporting
Cristin:	Current Research Information System in Norway
EBM:	Evidence-Based Medicine
ExDS:	Excited Delirium Syndrome
GP:	General Practitioner
HIV:	Human Immunodeficiency Virus
ICMJE:	International Committee of Medical Journal Editors
IMRAD:	Introduction, Methods, Results And Discussion
ISI:	Institute for Scientific Information
RCT:	Randomised Controlled Trial
MI:	Myocardial Infarction
REC North:	Regional Committee for Medical and Health Research Ethics North
UNN:	Universitetssykehuset Nord Norge (University Hospital of North Norway)
WPA:	World Psychiatric Association
JIF:	This is one measure of journal quality. The Journal Impact Factor measures the average number of times that articles published in a specific journal in the two previous years (e.g. 2015 and 2016) were cited in a particular year (in this case 2017). Example of calculation: No. of citations received in 2017 for citable articles from 2015 and 2016, divided by the total number of citable articles published by the journal in 2015 and 2016 (University of South Australia, Library Home Page, 2020).

LIST OF ARTICLES

1. Nissen, T., & Wynn, R. (2014). The clinical case report: a review of its merits and limitations. *BMC Research Notes*, 7, 264.
2. Nissen, T., Bergvik, S., & Wynn, R. (2015). The case of case reports: a decade of publications by staff at a major university hospital. *European Journal for Person Centered Healthcare*, 3, 215-221.
3. Nissen, T., Rørvik, P., Haugslett, L., & Wynn R. (2013). Physical restraint and near death of a psychiatric patient: A case report. *Journal of Forensic Sciences*, 58, 259-262.
4. Bugge, E., Nissen, T., & Wynn, R. (2016). Probable clozapine-induced parenchymal lung disease and perimyocarditis: a case report. *BMC Psychiatry*, 16, 438.
5. Nissen, T., & Wynn, R. (2018). Clenched fist syndrome: a case report. *Journal of Medical Case Reports*, 12, 168.

ABSTRACT

Case reporting has been important for documenting and communicating medical practice and discoveries since Egyptian antiquity.

The history of the case report (CR) was shortly presented so as to ease the understanding of its contemporary role in medical writing. The fear of its extinction in the later years was described. The genre has been an important article type in the field of medicine for at least two-and-a-half millennia. Following the emergence of the Evidence-Based Medicine (EBM) movement, the role of the case report seemed threatened. In hindsight, concern about its imminent demise was unfounded. The case report has been, and still is, an important method for recording and communicating the observations and various kinds of clinical endeavours performed by physicians through history. Medicine in earlier times was to a large extent speculative, i.e. based on mere theories and ideas. These theories were often perceived as logical and rational within their cultural context, but were in hindsight dubious or obviously wrong. The practice of writing case reports may have balanced against the risk for overreliance on medical dogmas and theories.

The various merits and limitations of case reporting were extracted from the literature and presented separately in order of importance according to our subjective evaluation. The main merits were the ability to detect new observations, generate hypotheses, accumulate clinical data about rare disorders, do in-depth narrative studies, and function as an educational tool. The main limitations included the inability to produce quantitative epidemiological data, to prove cause-effect relationship, and to generalize.

In a bibliometric study, we analysed the frequency and other relevant quantifiable aspects of published case reports. We extracted data from a regional university hospital's production of case reports in a ten-year period. The main findings were (i) 2.2% of the total production of research articles were CRs, (ii) the mean number of authors was 4.4 per article, (iii) a dominance of male authorship, (iv) one third of the case reports was the result of a collaboration with other national hospitals or foreign hospitals/universities, (v) 43% of the titles lacked information about the genre (i.e. case report/series), (vi) practitioners within the specialties of neurology, rheumatology, plastic surgery and medical genetics published the most articles, (vii) 88% of the articles primarily achieved to further medical science while 12% had an educational aim, and (viii) one third were not cited at the time of data collection.

The thesis includes three separate single case reports. Two of these described cases were of somatic events, occurring in the wake of the treatment of psychiatric disorders. These events were physical restraint asphyxia in one patient, and concurrent clozapine-induced perimyocarditis and parenchymal lung disease in the other. The third case was a schizophrenic patient who developed a complication, the Clenched fist syndrome, while hospitalised for a hip fracture.

These three reports serve as exemplars of modern case reports. They comply with ethical and regulatory requirements for informed consent, confidentiality, genre specific requirements such as format, and for two of them (Article 4 and 5) the university policy for open access publication. They are notable educational alerts for clinicians and they present data that adds to the corpus of scientific evidence in their respective fields. Last, but not least, they illustrate the use of case reports that encompass both somatic and psychiatric symptoms and disease.

In sum, the thesis has a theoretical and an empirical part. The theoretical part is the condensed historical background presented in the summary of the thesis, and Article 1 presenting the description of the merits and limitations of the CRs. The empirical part consists of a bibliometric study focusing on the characteristics of published CRs over a decade (Article 2), and the three single CRs (Article 3-5).

The thesis describes the CR as a central and vital medical genre, with a very long history in medicine. It has a range of merits that have further broadened its appeal in recent years, but also some important limitations that should be kept in mind. Modern CRs, as those included in the thesis, tend to share some similarities, for instance in their structure, but can show much variability especially in their topics. While many CRs adhere to a strict biomedical approach, it is also possible to take a more biopsychosocial approach to CRs. The CR is likely to play an important part in medicine also in the future.

1. INTRODUCTION

I had the opportunity to meet Eysenck once, and I will never forget his devotion to statistical research. "You cannot have knowledge," he told me over lunch, "unless you can count it." What about the case report, I asked; is that not knowledge at all? He smiled and put up a single finger: "Even then you can count."

S. Nassir Ghaemi, "A clinician's guide to Statistics and Epidemiology in Mental Health", 2009.

1.1 Motivation

My interest in case reports and case reporting started in the mid-1980s when I as a junior doctor at the psychiatric hospital in Tromsø was overwhelmed by the amount and diversity of suffering and psychopathology among the seriously ill patients. Often I felt totally at a loss about how to understand and care for them. My mind was filled with a thousand questions that yelled for answers. Once I stopped one of the senior colleagues in the hospital corridor just to tell him about one of the latest clinical observations that had perplexed me.

"Why don't you write about it?" was his immediate response. "Is that possible?" I asked. "Yes, of course", he said, "just dig into the patient's medical record and collect the relevant data". So I did. Soon thereafter, colleagues and I succeeded in publishing two case reports and two case series (Nissen, 1987; Nissen & Haggag, 1987a; Nissen et al., 1987b; Nissen & Haggag, 1988). Three of these were in the psychiatric domain, presenting the phenomena of toxic psychosis secondary to antiparkinsonian drug overdose, coprophagic behaviour, and parasuicidal snow-wandering, respectively. The fourth was a case series on the treatment of obstructive sleep apnoe syndrome (Nissen et al, 1987b).

Having been a practising hospital physician for 38 years, I do not get surprised to the same degree when encountering reportable clinical phenomena. However, I still get the urge to work out a case report, preferably in collaboration with colleagues, when an idiosyncratic case turns up. The experience I have gained from the years of clinical practice as both neurologist and psychiatrist has made me aware of the importance of establishing rapport and alliance with

patients. Those skills are paramount when it comes to treatments where the therapeutic relationship is central, e.g. in long-term psychotherapy, but also when engaging and cooperating with a person who might be a candidate for a case report. Writing case reports requires other skills, too. You need the acumen to identify the out of the ordinary phenomenon, the “outlier”. In this regard, having met a lot of patients helps. That does not mean you have to be a senior physician. Reportable cases are often identified by junior doctors, simply because they typically see more patients in their day-to-day practice.

Furthermore, I think writing case reports – in unison with all kinds of research – requires an “objective”, detached scientific stance. If you have an idea about reporting a case there is a risk you might get fixated to a specific focus that is actually irrelevant or outright wrong. This is parallel to what sometimes may occur in clinical work: A therapist gets a hang-up on a rare diagnosis or a peripheral phenomenon and is thus led astray from the right path. Having more than one author working on the case report may be an antidote to this bias. If you are a team of authors, some of the other ones will be more detached and thus able to calibrate or correct the one that has the hang-up.

Another safeguard against being biased – for both clinicians and researcher – is adhering to the biopsychosocial model (Engel, 1977). Even though you think you have a full understanding of a case, you should not rest until you have examined the biological, psychological, and social dimensions of the case.

Some ten years ago professor Rolf Wynn encouraged me to take up on working with case reports again. However, this time I started writing not only a case report, but also researching and writing *about* the genre itself, that is, its historical vicissitudes, epistemology and applicability. So far this endeavour has paid off with seven publications (Nissen & Wynn, 2012; Nissen et al., 2013; Nissen & Wynn, 2014a; Nissen & Wynn, 2014b; Nissen et al., 2015; Bugge et al., 2016; Nissen & Wynn, 2018). From this collection I have selected five articles that illustrate some important aspects of the clinical case report and fit with the PhD format required by *UiT – the Arctic University of Norway*.

In this thesis, my aims are to add to the knowledge regarding the case report genre. I will do this in different ways. I will examine aspects of the history and current applicability of the case report genre (its merits and limitations). I will also present and discuss results from a bibliometric study on case reports at a major Norwegian psychiatric hospital. The main part of

the thesis is related to the three included case reports. These are exemplars of modern case reports within the field of psychiatry. They represent patients (or, cases) that have come to my attention as a practicing clinician (or – in one of the cases – to the attention of a colleague). The way of identifying and selecting patients that are eligible for case reports is very different from most other research designs. The case report is dependent upon a clinician observing something unexpected or something of particular interest. The CRs that I have selected represent clinically complex psychiatric cases and they include, to varying degrees, biological and psychological perspectives. As I will discuss, they differ much in their topics and the degree of biopsychosocial approach, they also share many features common to the case report genre.

1.2 Central terms

Medical writing comes in many forms. The case report is one of them. It is not a new invention. In 1968 the opening sentence in an article in the *Journal of the American Medical Association* went like this: “The case report is the archetypical medical article” (Roland, 1968, p. 83). The author proceeds by giving some practical advice to case report writers.

This thesis has a relatively wider scope. I will examine topics such as the function and role of the case report (CR) today and how it interacts with other formats/genres of scientific articles. I will attempt to explain the longevity of the CR and discuss other related topics that are relevant in order to understand the clinical case report genre.

My perspective in this thesis is primarily medical, i.e. that of a practicing clinician. Interestingly, and rather flattering for the field of medicine, scholars of various disciplines have studied medical literature in general and the case report in particular. Among these we find medical historians, linguists, scholars in literature, scholars in communication, and philosophers of science. From their outside, distanced perspective, they can make observations that physicians do not easily notice. We have in our studies drawn on and expanded on some of this prior literature (Rose & Corn, 1984; Hunter, 1991; Atkinson, 1992; Eriksen, 1993; Taavitsainen & Patha, 2000; Hurwitz, 2006; Berkenkotter, 2008; Álvarez Millán, 2010; Pomata, 2010; Ankeny, 2011; Salager-Meyer et al., 2013). From the medical field two well-written scholarly texts on the subject have been published (Jenicek, 1999; Packer et al., 2017).

First, some words on terminology seem apposite.

The Latin noun *casus* can mean “fall, overthrow; error; accident, chance, event; occasion; misfortune; danger, risk; death; (grammar) case” (*Pocket Oxford Latin Dictionary, 1994*).

Case in English has several meanings. In a medical or health related context it usually means a happening or an occurrence (*Taber’s Cyclopedic Medical Dictionary, 2009*).

Report has its Latin origin from the prefix *re-* (signifying back or again) and *porto* (carry, bear, convey). A report is something that is literally “brought back”, or a statement of facts given in reply to inquiry (*Nutall’s Standard Dictionary, 1898*).

Case report is defined by *Taber’s Cyclopedic Medical Dictionary* as: “A formal summary of a unique patient and his or her illness, including the presenting signs and symptoms, diagnostic studies, treatment course and outcome” (*Taber’s Cyclopedic Medical Dictionary, 2009*).

Case series: A case report with more than two cases. Usually 3-10 cases (Jenicek, 1999).

The case in a case report is, strictly speaking, the disease, disorder or clinical phenomenon being examined. It is usually not the patient or person with the affliction (*Taber’s Cyclopedic Medical Dictionary, 2009*).

Case history: This designates just the anamnesis, that is, what we end up with after having taken the patient’s history. Or more elaborately, according to Taber’s definition: “The complete medical, family, social, and psychiatric history of a patient up to the time of admission for the present illness” (*Taber’s Cyclopedic Medical Dictionary, 2009*). However, many use the term *case history* synonymously with *case report* or *case study*.

Case presentation: Medical journals often instruct authors to present the case as a brief description containing clinical and demographic details, the diagnosis, any interventions and the outcomes. An example can be found in the “Preparing your manuscript” guide of the *Journal of Medical Case Reports* (*Journal of Medical Case Reports, 2020*). Most journals publishing CR emphasise the importance of brevity, parsimony, clarity, conciseness and focus. There is often a limit on number of words and figures. The case presentation or description should contain only the clinical information (background, history, supplementary tests, course, etc.) that is directly relevant for the case report topic. The presentation should be focused, not comprehensive. The *Case presentation* is usually the “middle” section of a printed case report article – between the Background/Introduction section and the Discussion section.

Anecdote: When used in the field of health care, anecdote can have the same meaning as case report or case presentation, but it often has a connotation of being something insignificant or unscientific because of its rarity (Ropper, 2012). Anecdote is often used to designate a spoken, short story. Published case reports are rarely labelled anecdotes (Hunter, 1991, pp. 69-82; Greenhalgh & Hurwitz, 1998, pp. 202-211).

A case study is one of the qualitative study designs used mostly in the social sciences (sociology, anthropology, political sciences) and psychology (Hilliard, 1993; Yin, 2009; Crowe et al., 2011). The case in a case study is not necessarily limited to the disorder of a single patient or person. The case can denote a group, a community, a social incident, a situation, etc. A disease outbreak or a school shooting can be a case study. In medicine the term is sometimes used for studies on single cases that are prospective and involve a therapeutic intervention of some kind. The medical doctor and epidemiologist Milos Jenicek defined the case study as “[a] detailed descriptions and analysis of an individual case which explains the dynamics, pathology, management and/outcome of a given disease” (Jenicek, 1999, p. 23). Sigmund Freud’s published cases have been variously called case histories and case studies (Mahony, 1993; Hilliard, 1993; Dodes & Dodes, 2017). Some consider the terms ‘case study’ and ‘case report’ as synonymous (Taber’s Cyclopedic Medical Dictionary, 2009; Taavitsainen & Patha, 2000).

A vignette is “a brief evocative description, account, or episode” (Lexico UK Dictionary, 2020). In the medical field *clinical vignette abstracts* is used to denote “brief case reports formatted as structured abstracts” (Wiese & Mookherjee, 2017, p. 121). Clinical vignettes can also be used for didactical purposes to illustrate clinical phenomena in textbooks and articles (Gunderson et al., 2007).

The object for this thesis is the “traditional” or “classic” case report. It is variously labelled *medical case report*, *clinical case report*, *single-patient case report*, *single case report*. It is usually retrospective, descriptive and naturalistic. It is not a planned study.

Several variations have emanated from the “traditional” CR. One of them is the experimental and planned n-of-1 or single subject clinical trial (Guyatt et al., 1988; Lillie et al., 2011). This one and other variations of the case report, e.g. the simulated cases (Wynn et al., 2011) are, however, not included in this inquiry.

The contents of the CR are usually structured according to the four main sections: Introduction, Case presentation, Discussion and References. Most journals today instruct authors to put an

Abstract before the Introduction, and some also require a Conclusion-section after the Discussion. The title should indicate explicitly that the article is a case report or case series, most often by the term “a case report” following the main part of the title. This format is similar to the IMRAD (Introduction, Materials and methods, Results And Discussion) norm for other medical research articles. The style – as already said – of the CR is characterised by brevity and conciseness. Lois and Selma DeBakey in their guidelines for case reporting say: “A useful case report is factual, concise, logically organized, clearly presented, and readable” (DeBakey & DeBakey, 1983, p. 363). The Case presentation section which is the core of the report, represents the story or narrative told by the author(s). This storytelling part of the CR is one element that distinguishes it from other research designs (Lysanets et al., 2017).

The way of finding identifying and selecting case materials that are eligible for case reports is very different from most other research designs. The case report is dependent upon a clinician or several clinicians observing something unexpected. This is the start or first step in working out a report. This step will be elaborated in the second chapter, “Materials and methods.”

1.3 Some historical notes

The oldest preserved case reports are about 3600 years old. They originate from Egyptian antiquity. One such ancient papyrus from circa 1600 BC, the Edwin Smith Papyrus, contains 48 cases discussing disorders of the head and upper torso (Allen, J. P., 2005; Breasted, 1930). The cases are typological, i.e. they do not represent particular individuals. Here is an example of how a wound in the temple was handled:

CASE 20: A WOUND IN THE TEMPLE PERFORATING THE BONE

Instructions concerning a wound in his temple, penetrating to the bone, (and) perforating his temporal bone.

EXAMINATION

If thou examinest a man having a wound in his temple, penetrating to the bone, (and) perforating his temporal bone, while his eyes are blood-shot, he discharges blood from his nostrils, and a little drops ; if thou puttest thy fingers on the mouth of that wound (and) he shudder exceedingly ; if thou ask of him concerning his malady and he speak not to thee ; while copious tears fall from both his eyes, so that he thrusts his hand often to his face that he may wipe both his eyes with the back of his hand as a child does, and knows not that he does so, (conclusion follows in diagnosis).

DIAGNOSIS

Thou shouldst say concerning him : "One having a wound in his temple, penetrating to the bone, and perforating his temporal bone ; while he discharges blood from both his nostrils, he suffers with stiffness in his neck, (and) he is speechless. An ailment not to be treated."

TREATMENT

Now when thou findest that man speechless, his relief shall be sitting ; soften his head with grease, (and) pour milk into both his ears.

(Breasted, 1930. Permission to cite obtained).

We see here a clear structuring of the text (Breasted, 1930, pp. 283-287). The Egyptian physician, being both a doctor and a priest, sometimes had to combine practical knowledge with the magic, i.e. spells and prayers (Allen, J. P., 2005).

Hippocrates (460-377 BC), or more correctly the Hippocratic Corpus probably written by several authors, changed medicine significantly. Hippocrates was born in an era when diseases were thought to have supernatural causes (Tsiompanou & Marketos, 2013). One of Hippocrates' main achievements was the new conceptualisation of diseases as having natural causes. The main medical genres in the Greek antiquity were treatises, commentaries and aphorisms. The Hippocratic Corpus also contains case reports that are presented in the section labelled *Of the Epidemics* (The Internet Classics Archive, 2020). These are matter-of-fact objective accounts of patients' diseases, their courses, and outcomes. From Book 1, *Of the Epidemics* we can study the report of Melidia's illness:

Melidia, who lodged near the Temple of Juno, began to feel a violent pain of the head, neck, and chest. She was straightway seized with acute fever; a slight appearance of the menses;

continued pains of all these parts. On the sixth [day], was affected with coma, nausea, and rigor; redness about the cheeks; slight delirium. On the seventh, had a sweat; the fever intermitted, the pains remained. A relapse; little sleep; urine throughout of a good color, but thin; the alvine evacuations were thin, bilious, acrid, very scanty, black, and fetid; a white, smooth sediment in the urine; had a sweat, and experienced a perfect crisis on the eleventh day (The Internet Classics Archive, 2020).

This is a purely descriptive report of symptoms, i.e. violent pain, nausea, sweating, several signs and probably a good outcome, or in Hippocrates' words: "a perfect crisis". (It seems that in most of the good outcome cases Hippocrates uses the designation "crisis" to describe the turning point.) We are not offered any diagnosis or information about intervention. Neither is there a hypothesis as to the cause of the illness.

The Hippocratic cases are actually quite similar to the "case presentation"-section of the CR of today. However, those of Hippocrates lacked the "Background/Introduction" and "Discussion" sections. Despite this, the similarities (the meticulous observation, description of context, symptoms, signs, and course) appear more salient than the differences. By recording his observations Hippocrates challenged the predominant oral transmission of knowledge (Tsiompanou & Marketos, 2013). His theories and generalisations can be found in other parts, especially in the *Aphorisms*, of the Hippocratic Corpus (Hippocrates et al., 1817).

Another key figure, Galen or Claudius Galenus (129-200 AD), contributed with a large amount of medical texts (Galen, 1929, pp. 130-244). His case reports were allegedly stylistically very different from those of Hippocrates. He had a more conversational tone. He wrote from a first person perspective with himself actively taking part in the unfolding of events (Hurwitz, 2006). In contradistinction to Hippocrates, he included the patient's voice in the dialogue. This is nicely illustrated in this excerpt from Galen's "*On prognosis*", chapter 10, when he was called upon to treat the Roman Emperor Marcus Aurelius for indigestion:

"What happened in the case of the Emperor himself was really beautiful. His own opinion and that of the physicians of his entourage who had gone abroad with him was that some febrile paroxysm had begun. But they all proved wrong both on the second and third day, in the morning and on the third hour. (...). I declared that this was no onset of fever, but that his stomach was overloaded by the food he had taken, which had turned to phlegm prior to ejection. My diagnosis seemed praiseworthy to the Emperor, and he repeated three times in

succession: "That's it. It is just what you say. I feel I have taken too much cold food". And he asked what was to be done. I answered what I knew, and said to him: "If it were anyone else who was in this state, I should follow my custom and give him wine sprinkled with pepper. But in the case of kings like yourself, physicians are in the habit of giving safer remedies; hence it will be enough to apply over your stomach some wool impregnated with warm spikenard ointment." (...) Then he declared to Pitholaus that he had "one physician, and he was a perfect gentleman." Further, as you know, he keeps constantly saying about me that I am "first among the physicians and alone among philosophers." For he had already had experience of many who were not only mercenary, but also quarrelsome, conceited, selfish, and malicious ... ". (Brock, 1929, pp. 217-218).

Hippocrates and Galen were different personalities, which might also be reflected in their cases. Hippocrates was described as humble, while Galen allegedly was arrogant and bragging (Ghaemi, 2009a; Duffin, 2010, p. 14). History has depicted Hippocrates as practicing empirical medicine (i.e. that clinical observation precedes theory). The Galenic medical philosophy, according to Ghaemi, held that "...there is a theory, and it is right" (Ghaemi, 2009a, p. 249). Thus, if the theory is right, there is no need for empirical research. This dichotomization, however, is probably not sufficiently nuanced. Other scholars describe Galen as a follower of Hippocratic medicine (i.e. belief in the humoral theory) (Nutton, 2004). Furthermore, he contributed to increased knowledge "... in real factual content - clinical, anatomical, and physiological" (Brock, 1929, p. 25).

The time following the fall of the Roman empire was characterized by a stagnation in the field of medicine. Medical knowledge was probably handed down from master to apprentice (Kroll, 1973). After Galen's written texts no further case reports have survived in Western medicine until their reemergence in the 13th century according to medical historian Cristina Álvarez-Millán (Álvarez-Millán, 2000). Still, from around 1100-1200 AD there was probably a cultural climate conducive to the production of medical literature. Until then Galen's writings had been the authoritative medical texts in Europe.

In the European late Middle Ages and the Renaissance new medical genres, the *practica*, *consilia* and *observationes*, were the result of doctors collecting texts based on their clinical practice (Pomata, 2010; Pomata, 2014).

The *consilia* (from Latin singular *consilium* meaning “advice”), appearing in the 13th century, were a genre initiated by the Florentine doctor Taddeo Alderotti. The *consilium* was a written recipe, i.e. advice, sent to an individual patient on demand (Pomata, 2014). *Consilia* were thus collections of advice. The recipes were based on the prevailing medical knowledge at the time and the *consilia* did not represent new empirical knowledge. Medicine was at the time still mainly based on canonical texts from antiquity.

The *observationes* are described by the medical historian Gianna Pomata as “... a distinctly late-Renaissance genre, a specific product of humanistic medicine” (Pomata, 2010, p. 199). The *observationes* were collections of particular cases having been examined and treated. Pomata depicts the emergence of this genre as related to four factors of early modern medicine:

- A coexistence of several paradigms and theories, i.e. a lack of consensus, was an invitation to contradict and challenge other physicians’ views.
- The relevance of praxis was again emphasized.
- The importance of exchange of experiences and information, and “... especially the description of rare cases” (Pomata, 2010, p. 196).
- A new tolerance and preference for an informal, lightweight text that could be allowed to be impressionistic and hastily written.

A major factor for this change could have been the shortcomings of the Galenic medicine after the 14th century plague (Black Death) in Europe (Duffin, 2010, p. 20). Galen’s writings, still being the authoritative canonical medical texts, had not described this devastating disorder. As Duffin has pointed out: “In the Renaissance, spiritualistic and vitalistic explanations of the natural world lost credibility. Hippocratic observation was glorified, while rigid Galenism waned, ...” (Duffin, 2010, p. 73). The climate was ready for the reemergence of empirical medicine. The authors of the *observationes* were mainly town physicians and court physicians, i.e. those who saw the most patients (Pomata, 2010, p. 226).

Another aspect worth mentioning is the introduction of the movable type printing press in 1439 by Johannes Gutenberg that paved the way for mass-production of medical books (Bynum, 2008, p. 31).

After the reemergence of the CR in the late Middle Ages (1300–1500) and Renaissance (1400–1600) it has been an integral part of medical literature. In the next historical epoch, The

Enlightenment (around 1700–1820), case reports were frequently published in medical journals (Atkinson, 1992) despite several new methods to advance medicine (systematic experimentation, statistical methods, anatomical dissections). It seemed medicine was imbued with ideas of progress. The medical historian William Bynum characterized the Enlightenment as “... a time of impressive medical entrepreneurialism [and] busy optimism” (Bynum, 2008, p. 40).

Case reporting and other research methods prospered side-by-side. Case reports could include findings from new practices; such as autopsies (King & Meehan, 1973). By the end of the 18th century, more specifically in the year 1775, the *Edinburgh Medical Journal's* patient narratives had been conventionalized according to the structure below, according to the linguist Dwight Atkinson (Atkinson, 1992):

1. General patient information (+ complaint statement)
2. (Past history/origin-of-complaints discussion)
3. Details of author's original examination of patient
4. Initial treatment regimens and its immediate effects
5. (Second treatment regimen and effects)
6. Subsequent course of illness/condition
7. Minimal notice of outcome of illness/condition.

The article type that reported “single cases of disease” was the most common in the *Edinburgh Medical Journal* in the 18th century (Atkinson, 1992). However, the author does not present quantitative data on the proportion of the various genres. From early 19th century, the CR was often organized into sections (Atkinson, 1992, p. 349).

At the end of the 19th and early in the 20th century case histories had become an established method of record keeping and dissemination of medical knowledge, and the prominent case histories authored by Sigmund Freud appeared (Wynn et al., 2011; Nissen & Wynn, 2014a). These were long and elaborate accounts of psychoanalytic treatment. *Studies on hysteria* was

published as a book in collaboration with Josef Breuer in 1895. It contained five cases, among them the famous “Anna O”. Freud was apprehensive about the reception of the case studies as revealed by this confession in a discussion on the last case:

“... it still strikes me myself as strange that the case histories I write should read like short stories and that, as one might say, they lack the serious stamp of science. I must console myself with the reflection that the nature of the subject is evidently responsible for this, rather than any preference of my own. The fact is that local diagnosis and electrical reactions lead nowhere in the study of hysteria, whereas a detailed description of mental processes such as we are accustomed to find in the works of imaginative writers enables me, with the use of a few psychological formulas, to obtain at least some kind of insight into the course of that affliction. Case histories of this kind are meant to be judged like psychiatric ones: they have, however, one advantage over the latter, namely an intimate connection between the story of the patient’s sufferings and the symptoms of his illness – a connection for which we still search in vain in the biographies of other psychosis.” (Breuer & Freud, 1955, pp. 160-161). (Permission to reprint obtained).

In other words, the information gained from a longitudinal course of psychoanalysis, although compared to “short stories”, gives the psychoanalyst an access to the patient’s intrapsychic processes causing hysteria.

Does Freud really think it is possible to generalise from a single case? In another case history, “Dora”, some years later, he writes about the “incompleteness” of his analytic results: “It is, on the contrary, obvious that a single case history, even if it were complete and open to no doubt, cannot provide an answer to *all* the questions arising out of the problem of hysteria. (...) It is not fair to expect from a single case more than it can offer...” (Freud, 1953, pp. 12-13). I think these are humble and wise words. It appeared that he was well aware of the limitations of the case history/study.

While not going into a lengthy debate on the epistemological status of Freud’s theories, his case studies contributed to the genesis and further development of psychoanalysis, which again has had an enormous impact on the fields of psychology and medicine (Mahony, 1993; Storr, 2011; Nissen et al., 2014a).

Freud has also been credited with bringing back storytelling, the narrative aspect, to medical/psychological scientific texts (Hunter, 1991). In a way, he went counter to the general

trend towards a conventionalized structure of case reports (Taavitsainen & Patha, 2000). In 1930 he received the *Goethe Prize* for literature awarded by the City of Frankfurt (Storr, 2001). Receiving a *literary*, not a medical prize, is impressive as it conveys a message about the literary qualities of the total production of his psychoanalytic texts at that time.

In 1985 the *Journal of the American Medical Association (JAMA)* published a volume of 51 landmark articles as a celebration of its first 100 years (Meyer & Lundberg, 1985). Fifty of these altogether fifty-one articles were originally published between 1884 and 1968. (One article from 1899, *The Gynecological Consideration of the Sexual Act*, was considered too offensive at that time to be published.) Fifteen articles, i.e. 30 %, were either case reports (4 articles) or case series (11 articles). A study of publications from three major general medical journals over a 30-year period (1946-1976) found that 38% of the articles were case reports without any consistent change in the frequency (Fletcher & Fletcher, 1979). In a later study of the same three journals – *Journal of American Medical Association*, the *Lancet*, and the *New England Journal of Medicine* – the frequency of CRs fell from 30% in 1971 to 4% in 1991 (McDermott et al., 1995). Clinical trials had doubled in frequency. A similar trend was found in other medical journals (Pincus et al., 1993).

Around 1970 the genre had become less popular among journal editors. There was a controversy as to the need for publishing medical case reports. In the following section we will describe this controversy.

1.4 The debate

In order to illustrate some of the conflicting arguments, in the following we have a brief presentation of some segments of a debate that occurred in 2004–2005 in the *British Journal of Psychiatry*. A shorter summary of this debate was presented in my article ‘The recent history of the case report: A narrative review’ (Nissen & Wynn, 2012).

In 2003 the retiring editor of the *British Journal of Psychiatry*, Greg Wilkinson, made a provocative statement regarding his achievement as an editor during the last decade: “I hastened the demise of the case report, to exclude what I see as psychiatric trivia...” (Wilkinson, 2003, p. 465). This spurred a heated debate with a range of letters to editor addressing the topic. D. D. R. Williams was the first to respond: “... while I suspect that academic/research colleagues

will be happy with [Wilkinson's] stewardship, many clinicians are likely to have some reservations (...) The nomothetic approach takes precedence while the detailed study of an individual patient is marginalised as trivia" (Williams, 2004, p. 84). He ended his letter to the editor with an appeal: "Psychiatry needs to return to its core values. (...) It needs to place the care and treatment of the individual patient centre-stage. Students, young doctors and psychiatric trainees must see at first hand the fascination and reward of working with patients, and see that the work is attractive and satisfying. A part of this process must be the rehabilitation of the detailed case report" (Williams, 2004, p. 84).

Another discussant asked: "Do our patients have loves, hates, hopes, fears, passions, fantasies, beliefs, hobbies, sports?" (Bourne, 2004, p. 455.). He answered the question himself: "A steady reader of the *Journal* would have no hint that they ever had. Consequently, if the new Editor wonders what improvements he might contribute, I suggest a more suitable name, the *British Mausoleum of Psychiatry*, unless there be changes in the *Journal* far more radical than in name. (...) Certainly bring back case reports, but also bring back the human being centre stage – the patients; families; psychiatrists, nurses; art, movement, group, and other psychological therapies; the whole therapeutic community, and people's lives. After all, why not? What else is the day-to-day practice of psychiatry about?" (Bourne, 2004, p. 455).

Next out is M. Ben-Ezra at Tel-Aviv University who takes a more balanced view (Ben-Ezra, 2004, p. 264). He praises the journal for having an editorial policy that encourages and accepts "... novel research that strives to the highest scientific and medical levels". However, he does not want to do away with the case report. So he suggests: "Instead of taking sides in the clash, it would be advisable to introduce a small section for the case studies where clinicians could share important insights about patients or unusual cases."

Shortly thereafter, the editor receives another letter – polemic and passionate: "Medicine generally is being dehumanised; if psychiatry follows suit, then we cannot complain that the masses are deserting us for alternative medicine. The bias of the *Journal* towards so-called 'pure science' while discarding the whole-person approach will accelerate the dehumanising process" (Enoch, 2005, p. 169). M. D. Enoch, the author of the letter, reminds the readers of the success of the book, *Uncommon Psychiatric Syndromes* (Enoch & Ball, 2001), which started with one case report. (Later editions contained several CRs.) His conclusion is: "The case history reminds us that the person is not merely a statistic but comprises body, mind and soul and that each must be taken into consideration for complete healing to occur".

The final letter-to-the-author in the debate was by M. Procopio who added a nuance to the rather one-sided defence for case reports (Procopio, 2005, p. 91). He distinguishes between "... two substantially different kinds of [case] reports". I quote: "The first group includes discussions of challenging cases with difficult clinical implications and interesting phenomenological descriptions, with the only aim to improve the readers' diagnostic and therapeutic skills." These reports he would welcome in the *Journal*. The other kind, however, "... have a substantially different objective. Their aim is to allow clinicians to share their anecdotal experience of unusual outcomes in clinical practice. These reports are a self-selected group of unlikely cases because only 'man bites dog' stories reach publication. (...) Anecdotal case reports can be confusing and misleading because the subjective data are often interpreted as objective, creating even more noise where the signal is already faint" (Procopio, 2005, 91). This kind of reports he thinks we can do without. The new editor of the *British Journal of Psychiatry*, Peter Tyrer, responded to this letter in a note by stating that the journal did "... publish case reports if they have, or could have, important general implications" (Tyrer, 2005, p. 91).

This brief review of a year long correspondence in 2004 and 2005 in a major psychiatric journal gives some hints to a change of climate regarding the status of the CR. The strife between the combatants was brought to an end. Today the existence of the CR is not threatened. How do we understand this oscillation from being devalued and dismissed to praise and popularity?

Some of the dismissive attitude towards the CR could be explained by the emergence of evidence-based medicine. Case reports had to step aside to let the new research articles get access to the journals. As the CR genre on average got fewer citations than large-scale quantitative studies, it had the potential of lowering the journals' Impact Factor (JIF) (Patsopoulos et al., 2005). The ranking of the CR on the evidence hierarchy was low (Patsopoulos et al., 2005). We cannot eliminate the possibility that case reports – often written by young, inexperienced physicians – were of a lower quality than other research articles and therefore more often rejected by journal editors (Nissen & Wynn, 2012).

As explicated in my article *The recent history of the case report: A narrative review* (Nissen & Wynn, 2012), from the late 1990s the CR genre was again wanted – not only by the readers – but also by the journal editors. Among the probable factors responsible for this change, I will draw attention to these: A fascination with narratives and qualitative research (cf. the "narrative turn"), scepticism against the EBM movement, a desire for a 'humanisation' of medicine, a new longing for the intensive study of the individual case within psychotherapy research, journals

experimenting with new formats of CRs, the case report's intuitive appeal and high readability, and electronic publishing. A more comprehensive analysis of these changes can be found in Nissen and Wynn (2012).

1.5 What kind of research is clinical case reporting?

In the medical community there have been various points of view concerning the case report's status as a medical text (Nathan, 1967; Nahum, 1979; Morgan, 1985; Coccia & Ausman, 1987; Morris, 1989; Squires, 1989; Martyn, 2002; Leduc, 1996; Godlee, 1998; Aronson, 2003; Rosen, 2008; Mahajan & Hunter, 2008; Bardhan, 2008; Scott, 2009; van der Wall & Wilde, 2009; Kidd & Saltman, 2012). Some considered CRs as trivia that should be removed from the medical journals (Wilkinson, 2003). Others praised it for its unique qualities – scientific or other (Vandenbroucke, 1999).

Before stepping into this controversy, there is a need to first take a step back in order to contextualize the CR. A relevant question is: What is medicine? Few would dispute that medicine is an applied science. In the medical community it is often stated that medicine is both "an art and a science" (Reese, 1999). The human being is more than an object of study for the natural sciences. Doctors and other health care workers profit from having some education, knowledge and attitudes from philosophy, the humanities, and the social sciences. What physicians and other health care professionals do is only partly based on facts, truths, and evidence gained from scientific research. A large amount of what they actually do during a working day is not based on evidence or scientific knowledge gained from research. An anaesthesiologist described his field, anaesthesia, in this manner: "Whilst anaesthesia must have a strong scientific basis, the fact that it is a 'doing', rather than a 'talking', specialty is inescapable. In common with surgeons, we are artisans. Craft must go hand in hand with science. Much of what we do can only be learnt during apprenticeship, in the operating theatre, the labour ward and the intensive care unit" (Mason, 2001, p. 100). The so-called "art" dimension of medicine supplements the scientific or evidence-based part of medical practice. Medicine at the bedside is an amalgamation of care and cure. Doctors, nurses and other health care workers have to make rapid decisions based on the available, often limited, data and knowledge. Health care is shaped by compassion, knowledge, sound judgement, technical skills, communication skills and ethical concerns. Furthermore, health care must be

individualized. In recent years medicine has made major progress. More patients profit from EBM, which has become the prevailing ideology or paradigm for scientific progress (Naylor, 1995; Enkin & Jadad, 1998; Browman, 1999; Greenhalgh, 2001; Kulkarni, 2005; Djulbegovic et al., 2009; Nierenberg, 2009; Dartmouth Library, 2020; The centre for evidence-based medicine, 2020). Despite this progress, a large amount of what health care workers do is still not evidence based. Therefore the literary scholar Kathryn Montgomery Hunter is maybe justified in her humbling description: "Medicine is not a science. Instead, it is a rational, science-using, interlevel, interpretive activity undertaken for the care of a sick person" (Hunter, 1991, p. 25).

In the applied science of medicine there is a large production of medical literature that comes in various forms or genres. The CR is one such genre. It can be dichotomized into two categories. Firstly, those who aim primarily for advancing scientific knowledge. Secondly, those who primarily have an aim of education and training. This second type of CR is used to teach or remind the audience about known, but rare phenomena or occurrences.

Case reporting has strengths and limitations. The Canadian epidemiologist Milos Jenicek, one of the genre's advocates, has described it as "... a kind of neglected orphan of medical research" (Jenicek, 1999, p. 27). Medical literature on research, as already mentioned, has been parsimonious when it comes to describing the methodology of case reporting (Sackett et al., 1985; McCarthy & Reilly, 2000; Kahn & Thompson, 2002; Chelvarajah & Bycroft, 2004; Taylor, 2005; Fletcher & Fletcher, 2005; Tolwani et al., 2006). There are various points of view as to whether the CR should be classified as qualitative research or not (Berkenkotter, 2008; Greenhalgh, 2002; Malt et al., 2012). It does not fit easily in the qualitative-quantitative dichotomy. Knowledge gained from a single individual is *idiographic* whereas knowledge gained from several cases, as in quantitative research, is labelled *nomothetic*. (The idiographic pertains to the particular person only, and is, in principle, not generalisable. The nomothetic knowledge is generic, common, pertaining to what is universal for the group.) Jenicek contends that case reporting shares many of the characteristics of qualitative research (Jenicek, 1999). When examining a patient, the clinician-researcher uses components of qualitative research, i.e. search for meaning. The patient's story is a narrative that is qualitative in the sense that it contains information that cannot (easily) be transformed to numerical or hard data. The quantitative part of case reporting, still according to Jenicek, consists of the hard data (also called clinimetric data) elicited during examination and work-up (e.g. blood pressure, pulse, temperature, laboratory tests, rating scales, etc.).

One of the main differences between what is usually considered quantitative research and case reporting might best be explained by how knowledge is inferred. In quantitative research the reasoning is usually *deductive* (from hypothesis to experiment), whereas in case reporting and qualitative research it is *inductive* (from single observation to theory or hypothesis). In case reporting the hypothetico-deductive method cannot be applied simply because there is no initial hypothesis. The hypothesis develops or emerges after the novel observation. It is the end product, not the starting point. The hypothesis that is generated can be a stimulus for further studies with other research designs. These studies might strengthen or weaken the hypothesis generated by the CR. Thus, the CR can be a part of a longitudinal research process – or in Jenicek’s words, “the first link in the chain of evidence” (Jenicek, 1999, p. 43).

The table below (Table 1) is a preliminary attempt to position the case report/case series in the landscape of research methods. It offers a bird’s-eye view of the characteristics of the main research methodologies used in medicine, i.e. the qualitative and the quantitative, with case reporting placed in the column in the middle. There is much variation in the design of qualitative studies, quantitative studies and CRs. The table must therefore be considered as a simplification that is based on ‘typical’ examples of the different types. Moreover, the table should be understood as a basis for discussion and not as an authoritative and final classification as there is considerable room for debating it.

Case reporting and qualitative methods share some characteristics. The CR can, among other things, focus on the patient as an agent handling his or her illness in collaboration with the health care system. Other similarities with the qualitative methods are the idiographic perspective, the data being ambiguous (open to interpretation), the non-random sampling and last but not least, the ability to generate hypotheses.

Which characteristics do the CR genre and quantitative methods have in common? They both handle the patient as a biological organism, a body. Data used for research are most often quantifiable/measurable. Data in a CR can for instance be temperature or blood pressure. (Or if the study object is a population as in quantitative research, individuals from the population are the source of numerical data.) Quantitative methods can generate hypothesis although not to the same degree as CRs and qualitative methods.

Table 1. Characteristics of the CR genre, qualitative research and quantitative methods

Characteristics	Qualitative research	Case reporting	Quantitative research
Study object			
The human biological organism (natural science)		+	+
The social world, subjective meanings and intentions (social science, humanities)	+	+	
Design			
Prospective	+		+
Retrospective	+	+	+
Planned study	+		+
Experimental (i.e. controlled)			+
Naturalistic (i.e. uncontrolled observations)	+	+	+
Data			
Ambiguous (open to interpretation)	+	+	
Objective ("hard" data, numerical, quantifiable)		+	+
Sampling			
Representative (random)			+
Purposive (non-random)	+	+	
Mode of knowing/reasoning			
Inductive	+	+	
Hypothetico-deductive			+
Hypothesis testing			
Support hypothesis			+
Disconfirm hypothesis	+	+	+
Generate hypothesis or theory?	+	+	+
What kind of knowledge?			
Nomothetic			+
Idiographic	+	+	

The table above is a tentative comparison of the case report with the quantitative and qualitative methodologies. The + *sign* indicates that the characteristic feature in the left column usually is present for the respective research methodologies (Quantitative, Qualitative, Case reporting). E.g., qualitative research typically deals with the social world, subjective meanings and intentions, but not with the natural sciences.

An *empty cell* indicates that the “Characteristic” is not typically associated with the research method. For example, “Prospective design” is not part of the classic case report-method. (Except for the n-of-1 trials that can be prospective and planned.)

As can be seen, the CR has similarities and dissimilarities with both qualitative and quantitative research methods.

1.6 From the biomedical to the biopsychosocial model?

Doctors are trained in analgesia,

but not in meaning.

Athar Yawar, The Lancet, October 11, 2008.

Modern medicine has been accused of being too biological, hence the designation “biomedical model” (Engel, 1977; Engel, 1980; Malt, 1986). In 1977 a landmark article written by the American physician George L. Engel appeared in *Science* (Engel, 1977). He described the state of things thus: “The dominant model of disease today is biomedical, with molecular biology its basic scientific discipline. (...) It leaves no room within its framework for the social, psychological, and behavioral dimensions of illness” (Engel, 1977, p. 130). He then proceeds to argue for a new model, which he labels the biopsychosocial model (BPS model). Although this model has been met with some criticism (Ghaemi, 2009b; Ghaemi, 2010), Engel’s model was to a large extent welcomed. As an example of its impact in the field of psychiatry in Norway, the major psychiatry textbook, *Lærebok i psykiatri (Textbook of psychiatry)*, has devoted a full chapter on the BPS model (Malt et al., 2012, pp. 131-138). In 1990 the majority of medical schools in the USA had adopted the BPS model as a basis of their teaching according

to the American psychiatrist Nassir S. Ghaemi, (2010, p. 41). Despite this, by 2010 the biomedical model was still the dominant one in general medicine in the USA according to Ghaemi, (2010, p. 45).

Engel contends that the biomedical model does not acknowledge that "... the behavior of the physician and the relationship between patient and physician powerfully influence therapeutic outcome for better or for worse" (Engel, 1977, p. 132). Many would say that the relationship effect is common wisdom, but still it is easy to forget this if you fixate your attention only on the biological pathology. The physician should not forget her or his role as "educator and psychotherapist" (Engel, 1977).

George L. Engel's ambition was to make the BPS model a conceptual framework for clinical work and medical science. In the following, I will present a made-up clinical vignette that in part draws on my imagination and in part represents an amalgamate of some of my cases. As such, it does not represent any actual patient, although the clinical vignette could be a real one. The purpose of this vignette is to illustrate the application of the BPS model in clinical practice.

A clinical vignette

Mr. Hansen and Mr. Olsen, both married men in their late 60s, were close neighbours living only 50 meters apart in the countryside. One afternoon Mr. Hansen got acute excruciating, substernal pain radiating to his left arm. The seasoned general practitioner, dr. Johnsen, had for almost 30 years been the family doctor for both households. He was called upon and made a home visit to Mr. Hansen. Suspecting myocardial infarction (MI) the country doctor decided to hospitalise the patient. A week later dr. Johnsen learned that Mr. Hansen had died while in the hospital. The doctor visited the widowed Mrs. Hansen the next day, expressing his condolences.

Two months later, in the early afternoon dr. Johnsen got a phone call from Mrs. Olsen. She was worried about her husband who was not well. He complained about pain and "something in his chest". On arriving at the house of the Olsens, the doctor learned that Mr. Olsen thought that he could have got the same kind of heart condition as his deceased neighbour. He walked restlessly back and forth in the living room, making circular movements with his right hand over the left side of his chest. After a short physical examination of Mr. Olsen, the doctor,

accepting a cup of coffee, sat down on the sofa. During the calm conversation that followed, the patient revealed how he had become lonely after his neighbour's death. His wife added: "Frank misses him a lot. They were best friends". Mr. Olsen nodded silently while tears run down his cheeks. "You were best friends ...", the doctor repeated. "Well", Mr. Olsen said, "the last I saw of Magne was him being carried on a stretcher into the ambulance."

After a while the doctor asked how his chest pain was "right now". "That's strange, it is actually much better", he said. The doctor did not suspect heart or lung disease. He suggested Mr. Olsen should come for a consultation at the doctor's office the next day for some further tests and "I would also like to hear more about your friendship with Frank. How about that?" "That would be nice." "Do you want to bring your wife?" "No, I don't think that's necessary".

I will leave the vignette for the time being while allowing the reader to ponder on it. I will return to it in the Discussion chapter to demonstrate its relevance for the understanding of important aspects of the CR.

After Engel's achievement, other – not necessarily competing – models, movements or programs have appeared. *Narrative based medicine* (Greenhalgh & Hurwitz, 1998), and *narrative medicine* (Duffin, 2010, pp. 95-96) are some examples. The terms were not strictly defined by their inventors. The various contributors to these movements seemed to have an ambition to invigorate the narrative perspective. A common factor was dissatisfaction with the present state of affairs. For instance, narrative medicine should be a corrective to the physician-centred perspective on diseases. The patient's voice, i.e. his or her story, should be validated (Wynn, 1995; Wynn, 1998; Duffin, 2010). The Norwegian GP (general practitioner) John Nessa has proposed the *narrative conversation* (in Norwegian: 'den narrative samtalen') as a third kind of doctor-patient dialogue in addition to the consultative and the psychotherapeutic conversations (Nessa, 2000). The narrative conversation should be more personal than the ordinary consultation and psychotherapy sessions usually are. The doctor should be less of an expert, and more of a listener to the patient's story about her life, her own symptoms and worries. The patient's understanding of her life should be in focus. The doctor's attitude should be supportive. The conversation should be more open, unstructured and individualized than the two other kinds of conversations.

In the social sciences, there was a “narrative turn” at the end of the 20th century (Riessman, 2008, p. 14; Berkenkotter, 2008, p. 6). Narrative perspectives or ‘storytelling’ as a concept became popular in a range of academic disciplines – history, psychology, sociology, anthropology, sociolinguistics, etc. (Riessman, 2008, p. 17). Various professions (e.g. law, nursing, medicine, social work) have embraced the concept (Riessman, 2008, p. 17; Nessa, 2000). The British GPs Trisha Greenhalgh and Brian Hurwitz describe the various applications of narratives in diagnostic encounters, therapeutic process, education and research in the first chapter of their anthology *Narrative Based Medicine* (Greenhalgh et al., 1998, pp. 3-16). A core feature of the narrative approach in medicine is to appreciate the patient’s subjective story – expressed by her or him – *verbatim*, not paraphrased. This narrative or story is not the same story that the doctor elicits during the anamnesis, and subsequently presents in the medical record or as a *Case presentation* in a published clinical case report. Actually, they can be very different. The doctor’s version – usually the written account in the medical record – is the doctor’s story about the patient’s story. Nuances in the patient’s narrative might get lost. When writing the medical record, health professionals sometimes paraphrase or quote the patient’s story. An avantgarde medical ward at our Psychiatric department invites patients to write their own accounts of illness in the medical record (Stendal, 2016). Sick children can communicate their stories by making drawings in addition to telling and writing (Weinbren & Gill, 1998). The health professionals are not, however, exempted from writing their respective sections of the medical record. Patients’ first hand “illness scripts” can be useful for many reasons: The reader might be drawn into the patient’s subjective world and, in being there, she or he can see and “feel” how the illness affects the patient’s life. This may provide a vicarious experience. The reader might get a grasp of the meaning of the illness or health problem. If the reader is the doctor treating the patient, the doctor’s interventions can be adapted to the patient’s profile, preferences and particular needs.

Narratives, to the degree that they allow us to understand and sometimes improve the care of the patient, will often be so-called ‘*thick*’ descriptions (Geertz, 1973). In the first chapter of the book *The Interpretation of Cultures*, (Geertz, 1973, pp. 3-30) the anthropologist Clifford Geertz elaborated on the concept ‘*thick*’ description that he had borrowed from the British philosopher Gilbert Ryle (Ryle, 1971/1990, pp. 474-479). Paraphrasing Geertz, the object of ethnography was what lies between the “thin” description and the “thick” description. The thicker the description, i.e. the richer and more detailed with regard to relevant facts, the easier it would be

to make valid or meaningful interpretations about the culture under study. And not to forget, ethnography required all observations to be contextualised.

There is a parallel between anthropology and medicine. The two disciplines deal with humans and human behaviour. The concepts of “thick” and “thin” descriptions can also be applied to medicine. Arthur Kleinman, who is both a psychiatrist and an anthropologist, has argued for conducting “mini-ethnographies” for patients with chronic illnesses (Kleinman, 1988; Stenklev, 1990). One of his points is the recognition that “[m]aster ethnographers and clinicians, though their work is quite different, nonetheless tend to share a sensibility. They both believe in the primacy of experience. They are more observational scientists than experimentalists. They are strongly drawn to the details of perception” (Kleinman, 1988, pp. 230-236). The purpose of the “mini-ethnography” was to assist the clinician to come as close as possible to the patient’s illness experience. Of course, the clinician should also place himself in the position of relatives and significant others thus witnessing the illness from their perspectives.

It seems to me that the concept of “thick description” applied in a medical context and Arthur Kleinman’s “mini-ethnography” are not too different. Kleinman points to a fading tradition of writing books of insights into the care of patients (Kleinman, 1988, p. 227). His book, *The Illness Narratives*, might be seen as an attempt to revitalise that tradition, i.e. to encourage humane care.

Other fields of inquiry share the ideas and ambitions of the BPS model and narrative medicine. One such field is the so-called *person-centred medicine* which is a concept that “... emerged as a response to the organ specific, technical and fragmented medical treatment and care that has evolved during the last century in health care systems worldwide” (Snaedal, 2012, p. 1).

Another field is the *medical humanities*. This is a discipline described as “... a broad area of study and practice encompassing all nontechnical or ‘human’ aspects of medicine” (Hooker, 2008, p. 369). It emerged as a field of academic enquiry in the 1970s in the USA. A main goal of the medical humanities is “... the exploration of the intersection of medicine with traditional scholarly disciplines in the humanities – philosophy, history, literature and sociology. Here the medical humanities allow us to probe the delicate balance between scientific empiricism and critical thinking” (Hooker, 2008, p. 370).

All the above mentioned “movements” or models for improving clinical practice pull very much in the same direction. But how does this relate to the practice of case reporting?

In my opinion the quality of clinical practice and medical research would profit by being guided by the BPS model. In being holistic it encompasses the three dimensions – the biological, the psychological, and the social – with the potential to give a richer understanding of the patient’s illness. An apparently minor and “easy” diagnosis of a child’s “green stick” arm fracture can turn out to be the first indication of a troubled family involving maltreatment. Quote the musician Neill Young singing: “*There’s more to the picture than meets the eye.*” (From the song ‘*Into the Black*’ on the album “Rust Never Sleeps”, 1979).

Compared to other types of medical articles, the clinical CR is usually a short text. Journal editors and the audience expect a text that is brief, concise, accurate, and focused. Often there is a limit on the number of words, tables and illustrations. The editor of *Archives of Internal Medicine* informed the readership that “[o]nly a rare case report need to be longer than 700 to 900 words in length” (Soffer, 1976, p. 1090). The co-editor of the book *Writing Case Reports. A Practical Guide from Conception through Publication*, Clifford D. Packer, makes the point that: “In the introduction, brevity is important” (Packer, 2017a, p. 70). Later on – “The biggest mistake my students make (...) is putting too much information into their case descriptions. (...) The key to a good case description is focus: include only the parts of the history, physical exam, lab and imaging results, and clinical course that pertain directly to the case report topic.” (Packer, 2017a, p. 71). Regarding the Discussion section, he emphasises that one of the essential elements is giving a useful teaching point at the end: “A brief, aphoristic, and memorable teaching point to conclude the discussion” (Packer, 2017a, p. 79). This is all good in so far that the signal-to-noise ratio will probably be high, and the message becomes very clear. However, this genre, the so-called traditional CR, will not suit an author or authors who feel a need to publish observations that could profit from a more comprehensive, in-depth study with a broad biopsychosocial approach. For these authors another format, “the case study” as defined by Milos Jenicek, could be a good fit (see definition of *case study* on page 12 in this summary). Phillip G. Clark described the educational value of case studies in gerontology (Clark, 2002). Part of the popularity of the case studies came from the flexibility of the format, especially allowing the richness of data and the first person account of the resident. Sigmund Freud’s famous case histories fit rather well with Jenicek’s definition of a *case study* (Jenicek, 1999, p. 135).

It appears that many within the field of medicine prefer the “thin descriptions”, at least for clinical case reports, while many anthropologists advocate the “thick descriptions” when doing ethnography.

The clinical CR is the article type that comes closest to the individual patient. The story it conveys can be a singular, delimited biomedical observation or – in principle – it can be a broad biopsychosocial, longitudinal story of a complex case. This variability is a unique quality of the CR. It can be compared to a vessel that can carry whatever cargo is needed. It is hard to conceive of any health related phenomenon or event that cannot be illuminated in a CR.

1.7 Bibliometrics and case reports emanating from a university hospital

Bibliometrics has been defined as “the application of statistical methods to the study of bibliographic data” (*Merriam-Webster Dictionary*, 2020). It is a relatively young discipline, also labelled “scientometrics” and “the science of science” (Pendlebury, 2009).

The idea of a citation index for the sciences was conceived by Eugene Garfield in 1955 and materialized in 1963 as the Science Citation Index (Pendlebury, 2009). In 1976 the first Journal Citation Reports appeared as part of the Science Citation Index. It contained the *Journal Impact Factor* (JIF) for 1975 and appeared as part of the Science Citation Index (Pendlebury, 2009). Garfield also established the firm *Institute for Scientific Information*, abbreviated ISI.

In recent years bibliometric research has taken on in scientific literature (De Amici et al., 2000; Chen et al., 2007; Kang, 2010; Low et al., 2014; Salager-Meyer et al., 2013; Akers, 2016). Studies from this field can present information about trends in publishing practices. Issues to be dealt with can be trends in publication rates of various medical genres, or more esoteric ones, like: “Are articles with amusing titles more often cited than comparable articles with straightforward titles?” (Sagi & Yechiam, 2008, p. 1).

Bibliometric data can also monitor and analyze quantitative aspects of scientific activity at universities and various other research institutions. These data can be used to rank and monitor the development of scientific journals, universities, and researchers. The JIF is one such measure.

Some journals have documented their own publishing practice concerning CRs (Kang, 2010; Lundh et al., 2011). However, at the time of the study, we were not able to find bibliometric studies on case reporting originating from particular hospitals. Curious about what could be learned from extracting publication data from our own university hospital, we designed a study with an emphasis on “profiling” not the single CR, but the corpus of case reports. We chose to extract data that we thought relevant to our exploration. We wanted to examine to what extent our university hospital, i.e. the University Hospital of North Norway, published case reports. And if so, what their characteristics were, and from which medical specialties they originated? We wanted to examine if the CRs were cited and also if there was a gender bias among the authors.

1.8 Case reporting in practice

A research project is often initiated by a research team having identified a gap in the current knowledge in a field. This team then designs a study in the hope of getting an answer that could close the gap, or at least narrow it. This is not typical when it comes to case reporting. There is an infinite number of gaps, and neither clinicians nor the academic physicians go around pondering on all the subjects it would be useful or nice to know more about. But once in a while the unexpected, the anomalous phenomenon, turns up saying: “Hello! I have – or more correctly – I *am* a hypothesis, maybe even an answer, to a knowledge gap that you might never have thought about. I’ll tell you my story and you can have the pleasure of communicating it to the medical community.” The point is, as already mentioned in section 1.2, the traditional CR is not usually a planned study. Being an experiment of nature, it typically turns up unexpectedly and has to be dealt with once it reveals itself, or more correctly, once you observe it.

While working with this thesis, three cases, i.e. clinical phenomena, came to my knowledge. A patient hospitalised in a high-security ward came close to dying during a physical restraint episode. I did not know the patient beforehand, but colleagues of mine at the hospital suggested that someone ought to look further into this rare event. I was thus included in a team of four who did the additional research necessary for writing a CR about the incident. Apparently, there was uncertainty and controversy in the medical literature about the cause or causes of sudden unexpected death when persons in police custody or patients in health care settings were

physically restrained, especially in the prone position (Bell et al., 1992; Chan et al., 1997; Farnham & Kennedy, 1997; Karch & Stephens, 1998; Milliken, 1998; Cina & Davis, 2010). This uncertainty represented a knowledge gap.

The second case was a hospitalised, previously healthy, schizophrenic patient who presented flu-like symptoms shortly after clozapine treatment was initiated. Despite termination of the clozapine tablets, the patient deteriorated. He had to be transferred to the intensive care unit for further diagnostics and treatment. After a long and tortuous course, the patient recovered. The diagnostic assessment was described. Several years later we did a retrospective review of the case. We now had the advantage of having all relevant clinical data, we could consult relevant specialists, and we could do an up-to-date literature search.

The third case was a psychiatric patient hospitalised in the intensive care unit due to medical complications secondary to a traumatic hip fracture. As I worked part time as a consultation-liaison psychiatrist, I was called upon to do a psychiatric assessment of the patient. His atypical hand postures caught my attention. Unable to rid my mind of this “enigma”, I sought literature databases. A rare psychiatric syndrome described in 1980 had not reached the pages of the major psychiatric textbooks (Simmons & Vasile, 1980). A case report, mainly for educational purposes, seemed appropriate.

This short introduction is meant as a background for the later presentation and discussion of the case reports (Articles 3-5). They will be used to illustrate features, especially the merits and limitations, of clinical case reporting today. Therefore, we abstain from divulging further in the details of the reports now.

1.9 Aims of the thesis

The aims of this thesis were to further the science related to the case report genre and develop three case reports that further science by adding to the existing knowledge within their delimited areas (specified below). We will discuss and illustrate the value and applicability of clinical case reporting in medicine. We will attempt to achieve this by

- 1) giving a condensed overview of some aspects of the history of the case report genre in medicine (addressed in the summary, pp. 13-23).

- 2) presenting the case report's current state, its merits and limitations, that is, the applicability of the genre (addressed in Article 1)
- 3) presenting bibliometric data concerning publication of case reports from a university hospital (addressed in Article 2)
- 4) presenting three published case reports from the field of psychiatry, related to the topics of restraint asphyxia; clozapine-induced parenchymal lung disease and perimyocarditis; and the Clenched fist syndrome. While being illustrative examples of the CR genre, they also each represent scientific contributions to their respective fields, i.e. forensics, clinical psychopharmacology, and psychosomatics/dissociative disorders (addressed in Article 3-5).

1.10 Some ethical considerations

The authoring of medical articles based on humans requires close attention in particular to two ethical issues, that is, informed consent and confidentiality (Wilkinson et al., 1995). In 1995 the *International Committee of Medical Journal Editors* (ICMJE) agreed on a statement regarding the requirement for informed consent (International Committee of Medical Journal Editors, 1995). The informed consent derives from the right to privacy and confidentiality. The committee's new guideline recommended that identifying information should not be published "... unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed consent for publication" (International Committee of Medical Journal Editors, 1995, p. 1272). The committee admitted that complete anonymity would be difficult to achieve. However, data should not be altered or falsified in order to attain anonymity. Journals were urged to include the requirement for informed consent in their "Information for authors". Furthermore, it should be indicated in published articles that informed consent was obtained.

The author team of a CR is often the same one who is responsible for the medical treatment and care of the patient. This may sometimes represent a conflict of interests. If the author team has made a vital observation that ought to be disseminated to the medical community, but the patient or next of kin does not consent, the author team cannot fulfil its duties to both patient and society. The duty to the patient comes first.

From the perspective of the patient, it might be difficult to reject her or his medical doctor's request for permission to publish. The doctor–patient relationship is asymmetrical with a power differential in favour of the doctor. Therefore, the voluntariness of the patient in consenting could sometimes be questioned. It is imperative that doctors or other CR authors are aware of their duty not to put undue pressure on the patient or the next of kin. The author has to be sensitive and careful when asking for permission to work out a case report based on the patient's medical history or disorder.

2. MATERIALS AND METHODS

2.1 Article 1

The purpose of Article 1 was to get an overview of the merits and limitations of the format of CR. In order to do this we performed a review of the literature on the subject. In this narrative review we chose Taber's Cyclopedic Medical Dictionary's definition of a "case report": "A formal summary of a unique patient and his or her illness, including the presenting signs and symptoms, diagnostic studies, treatment course and outcome", although with two adaptations; we allowed for 1 or 2 patients in a case report (as *Taber's Cyclopedic Medical Dictionary* also does) and from 3 to 10 patients in a case series (in accordance with Jenicek's definition (Jenicek, 1999)). As there were no rules governing the number of cases in case reports and series respectively, our choice was a practical operationalisation. The study was delimited to the retrospective, naturalistic and descriptive case report, also labelled the "traditional" or "classic" case report. We excluded other types of "cases", among them planned, experimental cases and simulated cases (Wynn et al., 2007; Wynn et al., 2011). The literature was identified in PubMed and Google Scholar with the search terms "case report(s)", "case series report(s)", "case reporting" in combination with "medical", "clinical", "anecdotal", "review", "editorial publication policy", "methodology", "overview", "strengths", "weaknesses", "merits", "limitations". Additional references were found by examining the references obtained in the electronic searches. Furthermore, we consulted textbooks on research methodology, epidemiology, and scholarly literature written by linguists and researchers in literature and communication that had studied medical genres. We extracted the relevant data and grouped the various merits and limitations in rank order according to our subjective evaluation of their value and importance. As our research question was to present opinions on CRs, i.e. merits and limitations, the research data were texts, not numerical quantities. Therefore, we chose a style that fit with the narrative literature review. While narrative reviews often do not include a section describing the methods used (Cipriani & Geddes, 2003), we explicated the methods and the limitations in separate sections in the article.

2.2 Article 2

This is a retrospective, bibliographic and descriptive study of published case reports and case series from the University Hospital of North Norway (UNN) over the 10-year period from 2004 to 2013. (The term “bibliographic” in this context designates the selection of data compiled from a particular article type in a predetermined electronic data source.) All case reports, case report series and case report-abstracts published in peer-reviewed Norwegian or international journals registered in the Cristin-database (Current Research Information System in Norway, 2020) having at least one author employed at the UNN, were identified and examined. Cristin is a national database that all Norwegian University and Hospital employees are expected to use in order to register their scientific publications. Data generated from Cristin are used for various purposes, including to incentivize researchers, for instance in the form of research funding or sabbaticals, which also increases the researchers’ motivation to actively use the database. Cristin collects and allows access to information about Norwegian research for its institutional members that are the universities, colleges, public hospitals and other research institutions. Cristin provides an overview of the publication of scientific articles, scientific book chapters, scientific books etc. and their authors, to the extent that the academic and other research institutions comply with the requirement to register them. There is often also additional information about the publications, including abstracts.

Our aim was to get a description of the hospital’s current practice concerning case reporting. Therefore, we chose the retrospective time span 2004–2013 as this was as recent as possible to the start of the study, which was February 2014. Furthermore, we assumed that a 10-year period would contain a sufficient amount of data to capture the characteristics of the case report corpus. Other authors had presented data concerning CRs in specific *journals* (Fletcher & Fletcher, 1979; Pincus et al., 1993; McDermott et al., 1995; De Amici et al., 2000; Ang et al., 2001; Dauphinee et al., 2005; Kidd et al., 2008; Kang, 2010; Jacques & Sebire, 2010; Lundh et al., 2011; Salager-Meyer et al., 2013). This inspired us to search for some of the same kinds of data, although our data would be a hospital’s production, not a specific journal. We ended up with eight different characteristics in order to “profile” the CRs. Thus, the following data was extracted from each article:

- a) the number of case reports and series,
- b) the number of female and male authors,

- c) the gender of the first and the last author,
- d) the number of articles with local, national and international authorship,
- e) if the title indicated the case report genre or not,
- f) the medical specialty,
- g) whether the article was perceived as more educational or primarily aimed for advancing knowledge,
- h) the number of citations.

2.3 Article 3-5

The subjects presented in the three separate case reports (Article 3-5) were selected from the patients admitted to the hospital, i.e. they were all in-patients when they came to our attention. As case reporting typically depends on particular and unusual observations done during regular clinical practice, there were no preplanned or designed study protocols before the potential cases were identified. Patients with reportable conditions, events or complications do not present themselves on demand. Therefore, naturalistic and serendipitous cases must necessarily be subjected to analysis, elaboration and discussion *after* they have come to the clinician's attention. And so we did with our cases. They were worked out after having assembled the relevant data and after a follow-up period. For two of them (Article 3 and 5) the idea of reporting them was conceived of during the patients' hospital stays. The idea of reporting Article 4 came to the first author some years after the patient had been discharged. The peculiar presentation and course inspired us to search for similar cases in the medical literature.

The manuscripts were prepared according to the standard format of abstract, introduction, case presentation, and discussion. This format is a bit simpler than the IMRAD standard which is used in most experimental studies (Sollaci & Pereira, 2004). Naturally, before writing the case reports we had to figure out if they were noteworthy. Would they add to science by bringing new knowledge or information to the medical community? Or, did they represent a high degree of educational value? Did we have a clear understanding of which particular point we wanted to make for each of the cases? After having settled for writing the reports and obtained written

consent from patients (Article 3 and 4) or next of kin (Article 5), we had to extract supplementary and essential clinical data from the medical records and other sources of information (e.g. interviewing the hospital staff, relatives). Finally, we had to exclude all information that was not required to highlight the salient features of the cases.

The clinical presentations were based on the corpus of clinical information obtained during history taking, psychiatric and physical examinations, and relevant ("on demand") supplementary laboratory tests. The clinical conclusions or hypotheses were thus in principle quite similar to standard clinical work-ups. In other words, there was no specific research methodology qualitatively different from clinical reasoning guiding our reports. However, the case reporting deviated somewhat from the regular clinical work in the hospital. We had to subject the cases to a more thorough study of the particular elements reported. This was done by extensive literature reviews, reexaminations of the clinical data, collegial discussions among the authors and sometimes repeated anamnesis. Furthermore, we frequently consulted other psychiatrists or colleagues from other specialties (anaesthesia, cardiology, neurology, plastic surgery, pulmonology).

The third article describes a man in his mid-30s who was subjected to a take down and immobilisation as a response to his physical acting out in a high security psychiatric ward. While being fixated by several members of the ward staff he lost consciousness and stopped breathing. We followed these steps in working out the CR:

- a) Relevant medical literature was searched from major textbooks of psychiatry and forensic medicine, and medical databases, mainly PubMed.
- b) We obtained informed consent and interviewed the patient twice. The interview focused on his recall of the episode and his subjective experience, i.e. thoughts and feelings, from the time when he was physically restrained and to the moment of losing consciousness, and the course after having regained consciousness.
- c) We studied the medical record meticulously extracting relevant information.
- d) We obtained collegial assistance from specialists in cardiology, anaesthesia, and lung diseases. One of the authors was present during the asphyxia-episode and the subsequent resuscitation. As a "participant observer" she had first hand observational information as she

was taking part in both the immobilisation and resuscitation of the patient. Her information was a useful supplement to the medical record.

e) We wrote the article according to the journal's guidelines and requirements for publishing. As the journal accepted longer case reports, we could be quite detailed in describing and discussing the course of events.

The fourth article presents a 23-year-old man with schizophrenia who got flu-like symptoms approximately one week after starting treatment with the antipsychotic drug clozapine. He was transferred from the psychiatric ward to the intensive care unit for further examinations and treatment. The immediate tentative diagnosis was malignant neuroleptic syndrome, later to be superseded by bacterial infection, and finally by the combination of perimyocarditis and interstitial lung disease. We followed these steps in working out the CR:

a) We searched relevant medical literature from medical databases, including PubMed.

b) We obtained written informed consent from the patient.

c) We obtained collegial assistance from two cardiologists and a pulmonologist in separate meetings in which we reviewed and discussed the various differential disorders mentioned above. One of the cardiologists had been part of the treatment team during the hospitalisation and therefore had first-hand knowledge of the treatment course.

d) We studied the medical record including all relevant supplementary tests meticulously.

e) We wrote the article according to the journal's guidelines and requirements for publishing CRs.

The fifth article presents a 60-year-old schizophrenic man hospitalised at the intensive care unit after contracting aspiration pneumonia. After a request for psychiatric consultation, I noticed an uncommon posture of his hands. As this was beyond my previous experience and knowledge I joined forces with my supervisor. We set out to explore the medical literature for similar or identical cases. We were guided by two research questions: Firstly, is this a previously described disorder and if so, is there a treatment? Secondly, if not previously described or being a rare disorder, can our case add relevant information to the literature? We followed these steps in working out the CR:

- a) We searched relevant medical literature from major textbooks of psychiatry, neurology and hand surgery, and medical databases, including PubMed.
- b) We did a thorough and meticulous review of the medical record including all the relevant supplementary tests that had been done.
- c) I had frequent psychiatric visits and close collaboration with colleagues from several other specialties (neurologist, pulmonologist, hand surgeon) during the course, until the patient unfortunately succumbed to his many diseases. This collaboration was as it often is when a seriously sick patient is hospitalized: Frequent “on-demand”/spontaneous short clinical discussions with a focus on saving the patient’s life. However, the “hand problem” was in this context a minor challenge. Still, once it came to my knowledge I felt it had to be addressed, partly because it appeared to be a psychiatric/psychosomatic phenomenon, and partly because I was already strongly involved in the patient’s treatment. In the aftermath, i.e., after the patient had died, it was necessary to consult with a specialist in infectious diseases and a microbiologist in order to get a full understanding of the terminal course and various decisions that had been made.
- d) We obtained written informed consent from the next of kin.
- e) We wrote the article according to the journal’s guidelines and requirements for publishing.

2.4 Ethical approval

We obtained written, informed consent from the two patients in Article 3 and 4 and from the next of kin of the deceased patient (Article 5) for writing the reports. Confidentiality was respected as we disclosed only the demographic and clinical information necessary for the articles to be sound. The patients in article 3 and 4 were invited to read the manuscript before publication, but both of them declined. The next of kin of the patient in article no. 5 also declined reading the manuscript. The CRs were approved by the Hospital’s Data Protection Officer after learning that ethical approval from *The Regional Committee for Medical and Health Research Ethics North* (REC North) was not required for this type of CR.

3. RESULTS

3.1 Article 1

In Article 1 our objective was to assess the medical community's viewpoints on the merits and limitations of the genre. These were the major merits of case reporting: The possibility to detect and report new phenomena, symptoms, syndromes, diseases, etc; The ability to generate hypotheses; The function of pharmacovigilance (i.e. the early reporting of (rare) potential side effects); A CR may be the only possibility when other methods are not an option; Allowing emphasis on the narrative aspect (i.e. the in-depth understanding of the individual patient); And often a high educational value. The most important limitations were: A lack of ability to generalize from the case report; No possibility to scientifically establish a cause-effect relationship; A danger of over-interpreting the importance or consequences of the CR; A possibility of publication bias; A retrospective design that carries with it scientific and methodological limitations; And the distraction of the reader from more clinically relevant issues when focusing on peculiar or very unusual cases.

Even though CRs lost their central place in medicine in the 20th century, case reporting remains very popular. It is an essential part of the repertoire of research methods, particularly since it complements other methodologies. Moreover, it plays an important role as an educational tool. A revision of the standard medical case report format has been suggested in order to integrate aspects of the biomedical model with aspects of the narrative approach, but without much success yet. The future prospects of the case report genre are likely to be found in new applications, i.e. online case report databases and open access to these databases for researchers and clinicians.

3.2 Article 2

This study was performed to increase our knowledge about the publication of case reports and case series from a major Norwegian university hospital. In the ten-year-period from 2004 to 2013 the sum total of case reports, case series and case report-abstracts was 51, which amounts

to 2.2% of the total number of 2313 published articles. The main findings of the analysis were: Multiple authorships were common; There were more male authors than female authors (both as first and last author and in sum total); In one third of the articles, there was collaboration between researchers at different hospitals and nations; Forty-three percent of the titles lacked information that clearly showed they were case reports or case series; There were more CR representing certain medical specialities, such as neurology, plastic surgery, rheumatology, and medical genetics; Close to 90% of the articles were classified as non-educational (i.e. primarily scientific); A third of the articles were uncited at the time of the study.

3.3 Article 3

This CR was published in the Journal of Forensic Sciences. It has the following structure: abstract and keywords, background (not a separate heading), case report, discussion, and references. It contains 3, 262 words, excluding the abstract and the references.

Physical restraint is a last resort emergency measure to calm and control an agitated and/or aggressive patient. This procedure can cause injuries, and in rare cases the death of the patient. One of the pathogenic mechanisms is asphyxia, that is, lack of oxygen to the body/cells. We describe and discuss an episode of physical restraint and the immediate course after the restraint was terminated in a hospitalized man in his mid thirties. The patient, a former boxer and wrestler, was very strong and overweight. During a period of worsening of his psychotic disorder he became physically aggressive and had to be immobilized by the staff at the ward. He was taken down and placed by force in the prone, "spread eagle" position on the floor. He was kept immobile in this position by 10-12 members of the staff. Each extremity was fixated to the floor by two persons, while two had to lie with their torso over the patient's back. A junior doctor held his head and talked calmly to the patient until the patient suddenly became unconscious and lost respiration. Once the doctor and personnel noticed this alarming change, the weight on his back was lifted. Then he was turned around to the supine position, and cardiopulmonary resuscitation was started. In the course of 1-2 minutes he regained consciousness and respiration, and cyanosis was replaced by normal skin colour.

There are some case reports and series reporting fatal outcomes when persons are subjected to physical restraint. However, our case report is the first to describe a reversal of a condition that came close to a fatal outcome. Doubts have been raised in the medical literature about physical

restraint being able to cause asphyxia and a fatal outcome. Therefore this case, being a "natural experiment" (the incident itself was of course highly undesired by all) that probably came close to a fatal end, is of special interest as it sheds some light on the aspects of pathogenesis and pathophysiology during this kind of near fatal restraint.

3.4 Article 4

This CR was published in BMC Psychiatry. It has the following structure: abstract/keywords, background, case presentation, discussion, conclusions, (abbreviations, acknowledgements, funding, availability of data and materials, authors' contributions, competing interests, consent for publication, ethics approval and consent to participate), and references. A chest x-ray was also included. The main text excluding abstract and references contained 2, 215 words.

The primary indication of the antipsychotic drug clozapine is treatment resistant schizophrenia. Leucopenia, agranulocytosis, and myocarditis are well known side effects. A previously healthy 23-year-old Caucasian man with schizophrenia got flu-like symptoms seven days after clozapine treatment was started. Based on clinical findings and pathological blood tests, malignant neuroleptic syndrome was suspected. Clozapine was discontinued. Treatment with oral bromocriptine was started. The patient got worse with dyspnoea, low peripheral oxygen saturation, and bilateral lung parenchymal infiltration visualized on chest x-ray. Furthermore, echocardiography revealed a low left ventricular ejection fraction and pericardial fluid. As a result of these findings an infection was suspected, while the malignant neuroleptic syndrome-hypothesis was rejected. Thus, the treatment with bromocriptine was suspended, and an intravenous cephalosporin antibiotic was started. An extensive further work-up in order to identify an infectious agent was negative. Ultimately, the patient improved. On follow-up examinations he had a persistent cardiomyopathy. In retrospect, the most probable cause of this episode was comorbid clozapine-induced parenchymal lung disease and perimyocarditis. This particular combination of clozapine-induced side effects had, to our knowledge, not been reported by other authors. Thus, it seems important to make the medical community aware of this serious dual side effect.

3.5 Article 5

This CR was published in the Journal of Medical Case Reports. It had the following structure: abstract/keywords, background, case presentation (past history, present illness, the abnormal hand postures), discussion, conclusions, (abbreviations, acknowledgements, availability of data and materials, authors' contributions, ethics approval and consent to participate, consent for publication, competing interests, publisher's note), and references. There were also four photos included. The text included 4, 781 words, excluding the abstract and the references.

Rare disorders challenge our diagnostic skills. Clinical case reports can be very useful in detecting rare disorders and generating hypotheses and may give an in-depth understanding of significant educational value. The Clenched fist syndrome/psycho-flexed hand was reported at the beginning of the 1980s, but has still not been described in the major psychiatric textbooks. It is interesting that the phenomenon has been mentioned primarily in the literature on hand surgery.

We present a case that I, in the role of consultation-liaison psychiatrist, encountered in the Intensive Care Unit. A 60-year-old Caucasian man with schizophrenia had been hospitalised with a tentative diagnosis of cerebral insult. Medical work-up excluded this diagnosis, but disclosed a hip fracture that was operated on. The operation was technically successful, but unfortunately all attempts to physically mobilize the patient failed. The patient contracted bilateral lung emboli, aspiration pneumonia and suspect sepsis. On the 23rd day post-admission the curious phenomenon of bilateral clenched fists was observed. No plausible organic cause for this was found. The patient eventually died on the 44th post-admission day despite treatment with anticoagulant drugs and antibiotics.

The phenomenon was classified as Clenched fist syndrome (often abbreviated CFS) due to its similarity with cases presented in the medical literature (Mitchell Hendrix et al., 1978; Simmons & Vasile, 1980; Frykman et al., 1983). According to the "ICD-10 Classification of mental and behavioural disorders" in the *International Statistical Classifications of Diseases and Related Health Problems, 10th version* the syndrome should be diagnosed as F44.4 Dissociative motor disorder (World Health Organization, 1992).

I had the opportunity of following the evolving Clenched fist syndrome closely from post-admission day 23 until the patient died three weeks later. This allowed for presenting tentative predisposing and precipitating psychological factors causing the syndrome. Besides sharing our

published case with the medical community, we urged for more reporting and research on the disorder.

4. DISCUSSION

In the *Introduction* a condensed historical overview of the CR was presented as a background in order to ease our understanding of its prior and contemporary role and current applicability to medical writing. The oldest written case reports were Egyptian papyrus from 1600 BC presenting clinical handling of various physical traumas. The almost continuous presence of the CR from the era of Hippocrates (400 BC) to our time was described. An overview of the merits and limitations of the CR genre was presented. As bibliometrics has become a field that, among other things, can quantify research activity, we are in a position to study case report production and various aspects of this production. Thus, we extracted data from our university hospital's production of CRs over a ten-year period.

Last, but not least, three single case reports were worked out and published. These three are exemplars of modern CRs. While they vary in their topics, they follow the typical structure of CRs today. All three contain an abstract and keywords. They all have a brief introduction/background section (two with a separate heading and one without) followed by a presentation of the case. Next, there is a discussion, and in two of the articles there is also a conclusion, followed in all three by the references. Two of the CRs include pictures of the clinically central phenomena (a chest x-ray and clenched fists, respectively). The three CRs vary in length from ca 2,200 to ca 4,800 words.

Two of them were somatic adverse events occurring during the course of treatment of psychiatric disorders. The third case was a rare psychiatric phenomenon or disorder that developed in a schizophrenic patient hospitalised for a somatic disorder. The rarity of this phenomenon and its unique context justified publication as a contribution to science as well as an educational alert to the medical community. These three reports illustrate the use of interdisciplinary case reporting encompassing both somatic and psychiatric illness.

4.1 The merits and limitations and how they apply to Articles 3-5.

Article 1 is a broad, comprehensive review in which we have critically scrutinized the merits and limitations of case reporting that we found in the literature (Nissen & Wynn, 2014b). The table below (Table 2) shows the respective factors/items in order of importance according to our judgement as presented in Article 1.

Table 2. Merits and limitations (based on Nissen & Wynn, 2014b)

MERITS	LIMITATIONS
New observations	No epidemiological quantities
Generating hypotheses	Causal inference not possible
Researching rare disorders	Generalisation not possible
Solving ethical constraints	Publication bias
In-depth narrative studies	Recall bias
Educational value	Information bias
Low expenses	Overinterpretation
Fast publication	Emphasis on the rare
Flexible structure	Confidentiality
Clinical practice can be changed	Falsification not possible
Exercise for novice researchers	
Communication between the clinical and academic fields	
Entertainment	
Studying the history of medicine for future researchers	

Later, we will examine the items in Table 2 in more detail and find out to what degree they apply to the three case reports that form part of the present thesis (Article 3-5). However, as the explication of the items in Article 1 was somewhat parsimonious, it seems necessary first to elaborate a bit further on some of them.

New or rare observations

The case report can describe new phenomena; more specifically new diseases, syndromes, side effects, etc. (Carey, 2006; Léauté-Labrère et al., 2008; Ankeny, 2011; Sandu et al., 2016). Before AIDS (acquired immune deficiency syndrome) was characterised as a new disease, only the complications of the disorder were reported (Gottlieb et al., 1981). A prerequisite for such reports is diligent clinicians who can report the observations to the medical community. The almost unique ability of the CR to detect and report novelties is not a typical feature of most cohort studies or controlled trials. The strength of RCTs (randomized controlled trials) is their ability to eliminate or minimize bias and answer the question: Does this intervention or treatment have a therapeutic effect? The RCT, however, rarely generates new ideas. Case reports and case series often do, but – on the other hand – they rarely present strong scientific evidence.

Knowledge about ‘origin stories’ of diseases and syndromes is often inadequate or does not exist at all (Lie, 2007). Publication of case reports concerning new diseases is important not only for the present, but also for posterity. Examples of some important syndromes that have been described and given diagnostic labels in CRs are neurasthenia, shell shock, schizoaffective disorder and Munchhausen’s syndrome (Beard, 1869; Myers, 1915; Kasanin, 1933; Asher, 1951).

In-depth narrative case reports

Within somatic medicine case reports are usually short, to the point, accounts of a single phenomenon concerning the patient’s physical health. Within psychiatry, and the wider field of mental health, case reports can be of a different kind. They can often be much longer and elaborate, and not written according to the traditional medical CR-format (Introduction, Case presentation, and Discussion). These are in-depth, more narrative-styled studies, often labelled

case studies (Hilliard, 1993). It is a study type with many similarities to qualitative research that aims to understand human behaviour, intentions, fantasies and a range of psychological phenomena. Freud's case reports, often labelled "case histories", are examples of such (Mahony, 1993). While Freud considered that his findings represented generalisable knowledge, present day researchers within psychiatry and psychology regard the in-depth, detailed study as an idiographic approach with the aim of getting knowledge about the phenomena of meaning and intentionality for an individual or a group of individuals. Studies of this kind – used widely in social sciences, the humanities, and to some degree in psychology – should be considered legitimate research even though the findings cannot be subjected to statistical generalisations. The natural sciences strive for nomothetic knowledge, i.e. that knowledge gained from research should be generalisable. This is not so when it comes to idiographic research findings which are not primarily meant to be directly applicable to other individuals. However, the findings can nevertheless be relevant for other individuals in similar contexts. Within the general field of qualitative research the concept of generalisation is typically "substituted" with other validity criteria (e.g. authenticity, credibility, trustworthiness, transferability) (Cresswell, 2013, pp. 243-252).

Clinical practice can be changed

The findings from CRs can change clinical practice. This can be both negative and positive. Negative if the finding leads to an ineffective or harmful treatment being implemented. It can be positive if it leads to – by way of further confirmatory research – a more effective treatment. Or it can instigate the larger research community to search for an infectious agent causing a new syndrome (e.g. AIDS), as in the case of the fast and successful identification of the Human immunodeficiency virus (HIV) (Gottlieb et al., 1981). Having identified the agent, several effective drugs rapidly entered the market. This is an example of successful collaboration between multiple research centres/teams applying different research methods (Ankeny, 2011).

On the other hand, the story about the introduction of prefrontal lobotomy in clinical practice tells another story. The inventor of the method, the Portuguese neurologist António Egas Moniz, published a case series in the *American Journal of Psychiatry* in May 1937 (Moniz, 1937/1994). The three cases described had a very favourable outcome. However, these three patients were selected from a series of 18 lobotomized patients. The course and outcomes of

the other 15 patients were not described. It is not unreasonable to think that the three patients were not selected at random. Although this single article alone was not responsible for all the unfortunate lobotomies performed in the following years, it probably had a greater impact than it deserved. As such, it is an example of the deleterious consequences of case reports when not met with proper scepticism.

Among the limitations I will only elaborate here on the items *overinterpretation* and *falsification* items. The other limitations in Table 2 are sufficiently explained in Article 1.

Overinterpretation

The finding or phenomenon reported in a single case report or a small case series is often rare, sometimes unique, but can easily be misinterpreted as something that occurs often or calls for action (Jabs, 2005). This common inclination is described as "the anecdotal fallacy" (Charlton & Walston, 1998), i.e. the human tendency to be influenced out of proportion by trivial or insignificant matters. It could be considered a 'faulty generalisation'. The fallacy is in the minds of the audience, not inherent in the CR method itself. The clinicians' focus on the common and ordinary could be blurred by a too strong emphasis on the rare and/or exotic. In the discipline of clinical ethics the tendency of individual cases to distract our attention from general issues has been labelled "the tyranny of the story" (Callahan, 1996). Due to the strong emotional appeal evoked by individual cases, the audience might be bewitched or "tyrannised" (to use Daniel Callahan's terminology) at times.

Falsificationism

Samir Okasha, a philosopher of science, refers to Karl Popper's assertion that a scientific theory should be falsifiable (Okasha, 2002). This was a fundamental feature characterising a theory as scientific. This falsification criterion cannot be applied to CRs. The CR is an uncontrolled observation, an "experiment of nature". Being a spontaneous, uncontrolled occurrence it cannot be replicated. (Replication is possible when doing controlled experiments. Spontaneous occurrences cannot be replicated.) However, although nature cannot produce *identical* observations or "experiments", nature can come up with *similar* ones (although we do not know where, when and for whom). Take the example of the drug thalidomide that turned out to be

teratogenic causing congenital malformations. There were several published CRs containing a single or a few cases, and they all appeared over a short time span. The association between the new drug being given to pregnant women and a sudden increase in the incidence of malformations in their babies was so overwhelming that the medical community strongly suspected there had to be a causal relation, and not an arbitrary association (McBride, 1961; Ward, 1962; Coodin, 1962). The manufacturer "Destillers Company (Biochemicals) Ltd." announced the withdrawal of all drugs containing thalidomide from the market in December 1961 after receiving "...reports from two overseas sources possibly associating thalidomide ('Distaval') with harmful effects on the foetus in early pregnancy" (Hayman, 1961, p. 1262). D. J. Hayman was the managing director of "Destillers Company Ltd." In a letter to the editor of *The Lancet* he announced the retraction of the drug from the market 2 weeks before the Australian obstetrician William G. McBride's concerned letter was published in the same journal. Although the company described the evidence as "circumstantial" it felt it had "... no alternative but to withdraw the drug from the market immediately pending further investigation" (Hayman, 1961, p. 1262). The lesson is: If there is a sudden increase in the number of cases and a plausible, new risk factor is present, as in "the thalidomide story", the evidence that there is a causal relation can be strong enough to guide appropriate measures.

It should also be mentioned that a collection of published similar cases could be grouped and used for a case-control study, which is a study design at a higher level in the "hierarchy of evidence" (Guyatt et al., 1995; Grimes & Schultz, 2002; Guyatt, 2008, p. 10). A CR can start a research process in which various study designs, both quantitative and qualitative, are used. In sum, the lack of falsifiability does not invalidate the case report's contribution to science. Milos Jenicek emphasizes that the CR is often "... a first link in the chain of evidence" (Jenicek, 1999, p. 29). Further studies, of various kinds, will either strengthen or weaken the hypotheses generated by the "first link" CR (Jenicek, 1999; Ankeny, 2011).

In the following we will examine how the relevant merits and limitations apply to the three case report articles (Article 3-5).

Some merits and limitations of Article 3

Physical restraint and near death of a psychiatric patient, presents a critical incident that could have caused the death of the patient (Nissen et al., 2013). Sudden unexpected death is a rare but well-known adverse event that sometimes occurs when health personell resort to physical restraint (Nissen et al., 2013; Kersting et al., 2019; Wynn, 2004). In our case, a medical doctor plus several hospital staff were present during the critical incident, a was unique situation which allowed for precise observations during the whole episode of restraint. The event almost ended with the sudden death of the patient. If the patient had died, the most likely proximal cause would have been asphyxiation due to respiratory arrest. Three of the Hill criteria for causality – temporality, plausibility and experimental evidence – seemed present (Hill, 1965). There was a close temporal association of the physical restraint and loss of consciousness and respiration, i.e. temporality. A causal relationship between physical restraint and compromised respiration has been described by several authors (Reay et al., 1992; Nissen et al., 2013). It is undisputed that impaired respiration causing severe hypoxemia can be lethal, thus the plausibility criterion is fulfilled. The experimental evidence-criterion is fulfilled as there are experiments documenting compromised respiration when humans are exposed to physical restraint (Chan et al., 1998; Michalewicz et al., 2007; Krauskopf et al., 2008). There is, however, a controversy as to whether the degree of restraint is sufficient to cause hypoxemia (Chan et al., 1998).

Therefore, our naturalistic “experiment” adds to the relevant literature. Our observation does not generate a new hypothesis. We contend, however, that it adds credibility to the restraint asphyxia theory, i.e., a person placed in the prone-position with a load on the torso might die due to respiratory arrest.

The event described by us is probably so rare that it would be practically impossible to collect a series of similar situations (Maher et al., 2014). A planned multicentre observational study collecting similar naturalistic events does not seem feasible considering the low frequency of these events. It is also hard to conceive of an experimental study exposing voluntary test subjects to the same degree of physical restraint, inducing unconsciousness, and respiratory arrest. The risk of fatal outcome or psychological sequelae would be too high and such a study would therefore be unethical. However, being an experiment of nature there are no ethical violations involved in our case-reporting research.

Our case report presents a *rare, maybe unique, observation*. Thus, it has a double mission. It contributes scientifically by adding data and analysis relevant for the inquiry concerning physical restraint hazards as well as having *educational value*. The case is, however, not an *in-depth narrative study*. The perspective is mainly biomedical with only a minor account of the patient's subjective experiences during the event.

Expenses were low. The CR article was crafted by the authors partly during working hours, partly in our spare time. Publication was slow, however. Finding a journal willing to publish it took some time. This might have been, partially at least, due to the “hybrid”-like nature of the report. Did the article deal with psychiatry, somatic medicine or forensic medicine? Luckily, as the *Journal of Forensic Sciences* had no specified restriction on the length of CRs, we were allowed to elaborate a rich and detailed report.

Although the article was not primarily *educational*, in focusing on the hazards of physical restraint it had a pedagogic aspect. Adhering to the standard format for case reports was no obstacle for us. In other words, we felt no need for a more *flexible structure*. We cannot claim that the CR has *changed clinical practice*. Actually, it might have been criticizable if it had. But judging from other authors referring to the article, our observation is obviously still valued in the controversy surrounding restraint-related deaths (Zhu et al., 2014; Mu et al., 2014; Jauchem, 2015; Michaud, 2016; Kersting et al., 2019).

As concerns the applicability of the CR for *novice researchers*, two of the authors included in the authorship team (P.R. and L.H.) were for the first time collaborating on a medical article. From the list of possible merits our CR exemplifies seven of the 14 merit items: Rare observation, strengthening hypothesis, researching rare events/disorders, solving ethical constraints, educational value, low expenses, experience for novice researchers. We are not in a position to comment on the more peripheral merits, i.e. *entertainment* and the possible *value for future medical historians*, included in the complete list of the 14 merits (See Table 2.)

Below I will focus on the limitations of the case report genre for the present CR.

I assume CR writers in general do not pretend to produce *epidemiological data*. Our single case cannot inform us about the risk or incidence of restraint related deaths, neither in the hospital setting nor in the general population. However, if there is a clustering of cases in a short time

span, researchers from various fields will soon be alerted and start doing research, be it epidemiological, pathological, biochemical, microbiological, etc. As already mentioned, the reporting of HIV-cases in the early 1980s is illustrative of an international endeavour to solve the aetiology and treatment of this disorder (Gottlieb et al., 1981).

To prove *causal inference* from a single, naturalistic observation is not possible. This is a humbling truth that is often forgotten. But the Hill criteria, mentioned above, are helpful as they can strengthen or weaken the plausibility of a cause-effect relation (Hill, 1965). Above, we discussed the possibility for a causal relation between the physical restraint and physiological findings (unconsciousness and respiratory arrest).

Case reporting does not allow *generalisations*. Our case does of course not “prove” that all cases of physical restraint related deaths are due to hypoxemia. But from a clinical and commonsensical perspective we feel justified when contending there was a causal relationship between the physical restraint and hypoxemia in our patient. There is no reason we should not say that great concern and carefulness should *always* be executed when restraint of any kind is applied to patients.

Concerning *biases*: Our CR was “lucky” in being accepted for publication. Had the patient died, the story might neither have been written nor published. Psychological factors among the treatment team (shame, sadness, etc.) or ignorance might have prevented us away from thinking about the importance of reporting the case. Or, if we had worked out a negative-outcome CR, that is, had the patient died, journal editors might have rejected it as irrelevant or less interesting. As authors of the article we strived, of course, for publication. However, others could have argued against publication. We believe that the case being published was not an example of *publication bias*.

Recall bias was not a major concern in crafting this report as the clinician (L.H.) directly involved in the handling of the patient, had a very clear and vivid memory of the occurrence. Furthermore, the medical record contained detailed and relevant information. However, the patient’s recall might have been flawed to some degree due to his psychotic state and enormous stress while being restrained. To find out whether the CR was afflicted with *overinterpretation* and undue *emphasis on the rare*, we would need feedback from the readers. From the articles citing our CR we have not found comments indicating that this is the case.

Complete *confidentiality and anonymity* can rarely be granted. However, we were pleased to get the patient's informed consent to publish the CR. Confidentiality was respected as we disclosed only the demographic and clinical information necessary for the article to be sound. The patient in Article 3 was invited to read the manuscript before publication, but declined. The working out of the CR was approved by the Hospital's Data Protection Officer.

Concerning *falsification not possible*: Since a naturalistic observation cannot be *replicated*, we have to search for similar observations in order to obtain more empirical knowledge on the subject. As of April 2020 there is only one that we know of. This is a CR describing a suspect excited delirium syndrome (ExDS) in a man who had cardiopulmonary arrest while being physically restrained, but survived (Maher et al., 2014). Unfortunately, the cause or causes of restraint-related deaths still remain obscure. Another avenue to get more knowledge is to recreate a similar situation in a laboratory setting (Chan et al., 2004; Parkes et al., 2008), but this is of course beyond the scope of the present thesis.

Some merits and limitations of Article 4

This article presents drug induced perimyocarditis and parenchymal lung disease which are known side effects of clozapine. The clozapine-induced parenchymal lung disease, however, is rarely commented (Aldridge et al., 2013). Even more rare is the combined affection of the two organs, i.e. heart and lungs. Thus, *rare observation* and *researching rare disorders* items are illustrated in the article. The CR is also educational as it shows how clinicians work sequentially in order to establish the correct diagnosis, i.e. the *educational value* item. *Expenses* were low. The limitations of not producing *epidemiological data*, *generalisation*, *retrospective information*, and *falsification not possible* applies to all CRs.

Even though a causal inference cannot be shown in a CR (*the causal inference not possible* item), an association can be a hint to causality. Regarding the possibility of a causal relationship between the drug, i.e. clozapine, and the severe medical complications (later to be described as side effects), we applied the *Naranjo Adverse Drug Reaction Probability Scale* to the case. A score of 5 estimated the causation as “probable” (Naranjo et al., 1981). Thus, the item *causal inference not possible* may not be unequivocally valid in this case.

Regarding the items *publication bias*, *overinterpretation*, *emphasis on the rare*, and *subjectivity/information bias*, all of which are potential or “dynamic” limitations, we cannot know for sure if these were operative. As the patient consented willingly the *confidentiality* criterion did not hinder the publication.

Some merits and limitations of Article 5

This article about the *Clenched fist syndrome* illustrates the merits of presenting *rare observations*, especially for this disorder that was characterized by a shortage of medical literature. Due to abundant information and frequent visits to the patient a biopsychosocial hypothesis could be formulated. This hypothesis is idiographic, i.e. pertaining to this patient only. However, further cases with the syndrome can be compared to ours and examined for similar or identical possible causal factors. Thus, the *generation of hypotheses* is exemplified. For the time being, reporting single (or a few) cases seems to be the only way of gaining more data on the disorder (*researching rare disorders* item).

The case has both scientific and *educational value*. The working-out of the case was done partly during working hours, partly during spare time. Thus, *expenses* were low. The working-out of the article took 6 months. An additional 7.5 months went by until its review process was completed and the article was published. This is a relatively *fast publication* process for high quality scientific journals today, although some journals promise very fast review and publication.

However, today’s fast publications cannot compete with some fast publications in the 19th century. As an anecdote, let me draw attention to the surgeon Henry Jacob Bigelow’s article on the use of ether as a general anaesthetic in 1846 (Bigelow, 1846). In this article, a case series, he reports a successful operation performed on a patient in ether anaesthesia on October 16th in 1846. The article was published on Wednesday November 18th, 1846, in the *Boston Medical and Surgical Journal*, i.e. the forerunner of the *New England Journal of Medicine*. The time from the surgical operation to publication was 33 days. This was rather impressive, especially as the other 6 cases in the article were given anaesthesia *after* October 16th.

We felt a need for *flexible structure* (Agha & Rosin, 2010). Due to all the information necessary in the Case presentation-section, we deviated from the journal’s requirement of a single timeline

and no use of subtitles in this section. We presented text timelines, one for the serious general medical complications that caused the death of the patient, and a separate text timeline focusing on the clenching of the hands. We considered this the best didactic approach. Fortunately, the journal accepted this rather minor deviation.

I doubt that the article has changed clinical practice among colleagues. No novices took part in the writing of the CR. I am ignorant about the *communication between the clinical and academic fields* and *entertainment* items. Only time can tell whether the CR will be of any use for future *medical historians*.

The limitations of relevance for Article 5 were to some degree similar to those of Article 4. *No epidemiological information, generalisation not possible* and *falsification not possible* were all applicable. Regarding *publication bias, overinterpretation, subjectivity/information bias* and *undue emphasis on the rare*, we cannot know if any of these items were operative.

The limitation *causal inference not possible* was not unequivocally applicable. Somatic differential diagnoses were excluded during the diagnostic work-up. The hypothesized psychogenic explanation seemed reasonable. Arguing that a Clenched fist syndrome erupts spontaneously without somatic or psychogenic etiology would be far fetched.

The case was studied and documented meticulously *concomitantly* with the unfolding of the events. It could be argued that such a method is not typically retrospective the way probably most CRs are. Thus, the limitation of *recall bias* that can limit the value of retrospective studies was practically absent.

4.2 The bibliometric study

The design of this study, Article 2, was unusual as regards the study object, that is, the corpus of scientific publications emanating from a university hospital. Unfortunately, there were no relevant comparison studies from other hospitals. However, if this study were to be replicated at other hospitals or centres, interesting comparisons could be made. We did make some cautious comparisons with journals that had looked into their own bibliometric data concerning CRs (Kang, 2010; Lundh et al., 2011; Salager-Meyer et al., 2013).

Our hospital published one CR per 50 articles, or more correctly 2.2%. This is a low number. Regarding causes for this we can only speculate. We do not know how many submitted CRs were rejected by the journals. Reasons for non-acceptance could be lack of relevance or quality. Or maybe, as discussed in the article, the clinician-authors could have prioritized writing original research articles having a higher ranking on the evidence hierarchy and thus were more conducive to their academic advancement.

It could be a consolation that the median number of authors per article was 3 (the mean number was 4.4 authors) as this might be an indication that our hospital's practice is in accordance with other authors' research on the bibliometrics of case reports (De Amici et al., 2000; Lundh et al., 2011; Salager-Meyer et al., 2013). There is a trend towards an increasing number of authors per article for all medical article types (Pintér, 2013). Research having become more laborious and complicated, often requires teamwork. Therefore we rarely find single authorship in medical articles today.

There was a gender gap with male author dominance, both for first author and last, i.e. senior, author. This can possibly be explained, partly at least, by many female doctors having career pathways different from males. Childbirth, maternity leave, childcare and family life can be hard to combine with a concomitant clinical and academic career (Sidhu et al., 2009). The female doctor's career has been described as an M-shaped curve (Allen, I., 2005). The first peak represents the early years. This is – after a dip – followed by a second peak indicating a career pursuit in the later years when family duties are less demanding (Allen, I., 2005).

One-third of the CRs was worked out in collaboration with authors from other hospitals, both within and outside Norway. The multinational collaboration rate was 14%. A study of citations of *all medical* research articles emanating from our hospital in the period 2005-2011 showed international authorship in 38.1% (Piro & Aksnes, 2014). This is an undisputed positive development. Collaborations across different locations, national as well as international, can improve the quality of research and facilitate future international research projects. Articles with multinational authorship also appear to enhance citation impact (Low et al., 2014).

The proportion of articles not cited, which was one-third, should not be worrisome. CRs in general are cited less often than medical articles with other research designs (Patsopoulos et al., 2005). The study of Patsopoulos and collaborators found that less than 1% of CRs had more than 10 citations within 2 years after publication. Actually, two thirds being cited might be

considered a good, or at least, a fair number. An analysis of data from the *Institute for Scientific Information* (ISI) database found an uncitedness figure of 46.4% for medical articles published in 1984 (Hamilton, 1991; Hem, 2014).

Article titles should be informative both regarding contents and study design. Nowadays most CRs contain the “case report”-identifier in their titles, usually after the punctuation colon (:) that follows the text carrying information about the contents. For instance, our article *Probable clozapine-induced parenchymal lung disease and perimyocarditis: a case report* conveys unambiguous information about contents and article genre. The finding in the bibliometric study of as much as 43% of the CRs lacking adequate identification about type of genre was not impressive. In 2013 a group of researchers developed a checklist in order to standardise the format of case reports (Gagnier, 2013), the so-called CARE (CAse REport) guidelines. An Indian group conducted a study of adherence to these guidelines among 1178 PubMed-indexed case reports published in 2015 in Indian journals (Ravi et al., 2018). Only 12.1% complied with the guideline concerning title.

The specialties that produced the most CRs were neurology, rheumatology, plastic surgery and medical genetics. Altogether 27 CRs (53%) came from these four specialties. Neurology has been found to rank high on case reports accepted for publication in the *Lancet* (Coles et al., 2003; Kang, 2010). This could be an indication that the variety of clinical phenomenological manifestations in neurology easily attracts clinician-authors to work out CRs. The contribution from the other three specialties (rheumatology, plastic surgery, medical genetics) was possibly occasional. However, vigilant clinicians within these specialties keen on writing CRs, could also have been a causative factor explaining the overrepresentation.

Nine out of ten articles primarily aimed for advancing knowledge. It was a finding that contrasted with the *Danish Medical Bulletin* publishing 89% educational CRs (Lundh et al., 2011). Our hypothesis was that clinicians at the university hospital chose research-oriented CRs that might be understood as more meritorious than the educational ones (Nissen et al., 2015).

4.3 The biopsychosocial perspective

I think clinicians should embark on every new case report by putting on their “biopsychosocial glasses” and then strive for collecting data that is rich and examined in its context. Here I would emphasise, first of all, the importance of taking a careful and thorough history, sometimes doing it repeatedly, and in collaboration with colleagues. When sufficient information is collected, collateral information from family and other significant persons, supplementary tests, etc., should be added. It is better to have a surplus of information than being short of it. Clinicians taking diagnostic shortcuts – that is, skipping essential parts of the relevant history – might miss important information.

The clinical vignette presented in Section 1.6 (‘From the biomedical to the biopsychosocial model?’) depicts a man with chest discomfort, maybe pain, that the experienced country doctor rather confidently considers to be a physical (*biological*) manifestation secondary to grief, longing and anxiety (*psychological*) and thinning of his social network after losing a close friend (*social*). However, he does not invalidate the patient’s subjective feeling. The doctor carries out his work with a biopsychosocial “mind-set”. He has all three aspects of the BPS-model integrated in his holistic way of practicing medicine. With an empathetic attitude he exhibits clinical knowledge, communications skills, and wisdom.

What about our three case reports (Articles 3-5)? Do they adhere to the biopsychosocial model? The CR in Article 3 was not an exemplar of a CR with a strong biopsychosocial approach. The focus was narrowed in on the particular episode of physical restraint. There was no attempt to contextualise and understand the psychological or social factors leading to the episode. Only the basic psychiatric status was presented. The article being almost purely biomedical does not necessarily mean that it is of inferior quality. The purpose was to report a detailed course of asphyxia related to physical restraint that did not end fatally. This observation was important to report as it added information on the pathophysiology of physical restraint. If we had included a lot of information with a broad perspective to the already long case report, the sharp focus could have been blurred.

A description can sometimes become so “thick” (Geertz, 1973; Sørhaug, 1996, p. 36) or so rich that it becomes hard to elicit the essence of the story (Sørhaug, 1996, p. 36). Still, we may wonder: Could a more comprehensive kind of CR have been made? A biopsychosocial, retrospective inquiry of the course of events might have revealed hitherto unknown factors that

contributed both to his psychotic decompensation and acting-out behaviour. If such a study had been undertaken, the aim had to be redefined and allowed for a more speculative discussion and generation of various hypotheses. This would be different from the usual singular fact or statement presented in the traditional CR.

The CR in the fourth article (Bugge et al., 2016) was also a predominantly biomedical one. Apart from presenting the patient's diagnosis, which was schizophrenia, the article was practically devoid of psychiatric/psychological and social perspectives. It should be mentioned though that a strict biomedical focus in an article is not necessarily a reflection of clinical management of the patient.

The fifth article (Nissen & Wynn, 2018) described a course of events where the serious somatic disorders (hip fracture, bilateral lung emboli) were the major concerns for the somatic physicians. The psychiatric comorbidities (schizophrenia, delirium, and conversion disorder) were attended to by the psychiatrist. In addition to the strict psychiatric assessment, information about his social situation was collected from his devoted family. Thus, this CR included quite well the biomedical perspective and fairly well the psychiatric perspective. Some knowledge about his social situation was useful for the psychiatrist's understanding of the patient. While this case is neither a "thick description" nor a thoroughly "BPS informed" CR, it contains elements of what could be a comprehensive BPS approach to case reporting. The journal's acceptance for a long text made it possible to present a tentative psychodynamic understanding of the conversion, i.e. the clenched fists.

The medical CR is the article type that best reflects and illustrates clinical work with the individual patient. If the clinical work is carried out properly according to the BPS model, it should be possible to work out and publish "BPS-informed" case reports. Such a genre, or "subgenre", might be a satisfactory format for some complex cases in which there are no clear-cut conclusions. As clinical work requires tolerance for the inherent uncertainty of clinical medicine, there ought to be a similar tolerance for publishing articles that sometimes present questions rather than facts and conclusions.

I think that in addition to the traditional CR, it is possible to learn a lot from a "subgenre" of the CR that adheres more to the BPS model. The biopsychosocial approach can also be understood as an ideal that it may be difficult to live fully up to when working on a CR. To what degree a biopsychosocial approach can be adhered to may depend on different factors.

Some topics lend themselves more to such an approach, while other topics are more biological in their nature. For instance, a CR focusing on a newly described virus may need to concentrate on biological perspectives, while a CR describing some type of behaviour may open more for psychosocial perspectives. The instructions of the journal the authors are aiming for publication in may also be of importance. Some journals have strict restrictions on the length of CRs, and a biopsychosocial approach may require a lengthier CR. On the other hand, some journals specify that they prefer that the patient's perspective is clearly presented in the CRs.

4.4 Strengths and limitations

Two of the aims of this research project were firstly, to study the CR genre itself, and secondly, to write and present case reports that met modern standards for the genre. Concerning the study of the genre, would it not be wise to leave that to medical historians, linguists, literary scholars and philosophers of science? The question is rhetorical. Academics from the mentioned disciplines have done quite a lot of research from their respective fields and with their methods (Hunter 1991; Atkinson 1992; Taavitsainen & Patha, 2000; Álvarez-Millán 2000; Álvarez-Millán, 2010; Berkenkotter, 2008; Pomata, 2014; Ankeny, 2011; Salager-Meyer, 2013). Therefore, we delimited our study to the CR genre's role and applicability in clinical medicine. We felt comfortable leaving linguistic and literary inquiries to scholars from other fields.

CRs in general are not usually frequently cited, and this is also the case with the three CRs included in the present thesis. However, article 1 (Nissen & Wynn, 2014b) had a proximity to the clinical field that seems to have made an impact on the audience and had per April 2020 been cited by 172 Google Scholar indexed articles. This is an indication that the audience has found it useful. Thus, despite the shortcomings of our inquiry, it seems reasonable to assume that our endeavour to some degree has advanced the understanding of the CR.

Another strength of the thesis is the innovative approach of situating the CR genre itself as the protagonist. That is different from most research projects where the methods play the "minor role" of tools adapted to the needs of the projects. The three case reports in this thesis (Article 3-5) use arbitrary cases to illustrate generic aspects about the case report method, in addition to being valuable contributions to science.

The references to the history of the CR as well as its current context, gives a broad exposition of its clinical and scientific applications.

However, my positive regard for and enthusiasm about case reporting might have hampered my ability to take an objective stance while working on the thesis. Being aware of this personal bias, I discussed my various ideas and opinions with my supervisors who nicely put me back on track. In addition, I strived to be balanced and function as my own “moderator” as I studied the viewpoints and disputes between those who devalued and those who praised the CR.

Article 1

The methodology had limitations. We cannot be sure that we found all the relevant literature based on the chosen search terms. The search could have been more systematic and rigorous. However, after repeatedly searching relevant literature in the years 2010 to 2014 I learned that new publications on the subject did not add relevant data beyond what was already found. It seemed that a stage of saturation was reached.

We catalogued the various merits and limitations of case reporting in Article 1 in order of importance according to our judgement, starting with the most important. This was done according to our subjective evaluations, i.e. qualitative judgements. The method of ranking was thus not very robust with explicit criteria for “importance”. The transferability of the ranking could be questioned. Other academics or clinicians might have ranked the items differently based on their respective values and contexts. It should be added though that the most important achievement of the article is the comprehensive list of merits and limitations and the grouping of them in the two categories.

Article 2

As concerns the bibliometric article (Article 2), we presented a detailed Methods-section and a discussion on limitations in the final paragraph of the Discussion-section. This article, in being bibliographic, used data from a national register (Cristin). The register was launched in order to collect all research articles from the Norwegian universities, colleges, hospitals, and other research organisations. The register depended on the authors/research teams themselves to

report published articles. A register with such a liberal routine of collecting the relevant data is liable to miss some of the scientific articles. We cannot know how many articles were missing for the relevant period (2004–2013), but we assume it was few. Being acquainted with the Department of psychiatry at our hospital we know that there were no unregistered psychiatric CRs in the period. Furthermore, having one's scientific publication record in the Cristin register is meritorious. This is obviously an incentive to register articles.

The number of CRs was fairly low. Great caution must therefore be taken when inferring hypotheses. We did not have similar data from any other universities or other hospitals for comparison. Our findings cannot be generalised to other hospitals or institutions. Neither can we say anything substantial about trends within the 10-year time span (2004–2013). The study informed only on the current state of things concerning our local clinical research. Future research at this or other hospitals could profit from using the findings as a benchmark for replication studies.

Articles 3–5

The limitations inherent to the CR genre have been presented thoroughly in Article 1. I do not find it necessary to repeat them here. As concerns this thesis, the authors of the three CRs had no previous clinical experience with two of the reportable occurrences, i.e. restraint related respiratory arrest (Article 3), and the Clenched fist syndrome (Article 5). We had some experience with clozapine side effects, but not with the combination of cardiac and lung side effects (Article 4). Being inexperienced with some specific events or disorders can be a drawback. On the other hand, the first time you encounter a clinical event you are liable to work harder and more systematically in order to solve, i.e. understand and treat, the case.

It could be argued that a richer history taking/anamnesis might have disclosed additional information/findings. Regarding Article 3, the patient said in the aftermath interviews that he did not panic or fear that he was dying when he uttered "I can't breathe" during the restraint episode. How can we understand this? Being professional means that we sometimes have to accept less than optimal information. The patient's psychiatric disorder plus the critical medical situation obviously hampered the communication. The patient did not appear comfortable about talking at length after the episode. Accordingly, we did not push for an in-depth interview. However, had the patient accepted a series of conversations after the episode, we might have

learned more about how he experienced and remembered the traumatic situation. Did he have any psychological sequelae? If so, how did he cope with them?

Both the *biopsychosocial model* of George L. Engel (1977) and the *mini-ethnography* of Arthur Kleinman (1988) could have served as tools or frameworks for a deeper understanding or alternative hypotheses.

As concerns Article 5, the Clenched fist syndrome, both the soma and the psyche were attended to. Had the patient survived, the social aspect would probably have been dealt with as a collaborative project involving himself, his supportive family, the GP, somatic and psychiatric departments at the hospital, and community services including a social worker at the hospital. Elements to attend to could be housing, assisted living, nursing at home, social network beyond family, economy, and cooperation between community psychiatry and the GP. Still, a leaning toward the *mini-ethnography* or *BPS model* could have taught us more about the three case reports.

Finally, the three patients in Article 3–5 were all men. Others have investigated patients' gender in case reports (Allotey et al., 2017). They found a gender bias with 10 % more case reports dealing with male patients. A gender bias among the patients of CRs is a matter of concern as it conveys an implicit message to the medical community that “[m]edicine in males may be regarded as more main stream, more interesting, more indicative of what is a normal disease process” (Allotey et al., 2017, p. 6). It might be difficult or impossible for the authors and/or editors to recognise one's personal bias when selecting cases to be written or published. As concerns myself, I cannot say for sure that I was not biased as only male case reports were included in this thesis. However, when looking into the psychiatric case reports I authored with colleagues in the 1980s, there were four female and one male patient (Nissen, 1987; Nissen & Haggag, 1987a; Nissen & Haggag, 1988).

4.5 Future perspectives

After being downgraded as a research article in the second part of the 20th century, the CR now seems to be thriving more than ever. At the *WPA 17th World Congress of Psychiatry* in Berlin in October 2017 case report-symposia attracted large audiences. A lot of CR journals, most of

them open access, have been established since 2007 (Kidd & Hubbard, 2007; Akers, 2016). Editors of these journals eagerly invite authors to submit manuscripts.

There is a downside to the profuse publication that we did not recognize while writing the two historical articles and the one reviewing the merits and limitations (Nissen & Wynn, 2012; Nissen & Wynn, 2014a; Nissen & Wynn 2014b). Financial motives of publishers might lower the threshold for accepting articles (Nawrot et al., 2010; Hem, 2011). This might occur with all kinds of scientific articles, not only for CRs. However, the medical librarian Katherine G. Akers has pointed to a significant growth of “predatory” case report journals whose aim primarily is the collection of publication charges, and where the quality of the CRs may not be properly assessed (Akers, 2016). A large volume of published low quality case reports could thus make it harder to extract the relevant literature. The ‘signal-to-noise’ ratio could become too low.

Both Jenicek and Packer et al. – in their respective books – devote a final chapter discussing the positive trend and future prospects of case reporting (Jenicek, 1999; Packer et al., 2017). Jenicek focuses on the achievements gained in the decade preceding publication of his book in 1999. In his book he emphasizes three major aspects:

1. The CR having opened “...the gate to further more refined and more complete research” (Jenicek, 1999, p. 126).
2. The CR’s role in “... maintaining the human aspect of medicine and medical research” (Jenicek, 1999, p. 131).
3. Furthermore, he thinks that the CRs have contributed to an equilibrium between quantitative and qualitative research (Jenicek, 1999, p. 132).

Packer, in a recent addition to the literature on case histories, points to the future demand for literature on *personalized medicine*. Personalized medicine is “... an evolving field in which physicians use diagnostic tests to identify specific biological markers, often genetic, that help determine which medical treatments and procedures will work best for each patient. By combining this information with an individual’s medical record and circumstances, personalized medicine allows doctors and patients to develop targeted treatment and prevention plans” (Pritchard et al., 2017, p. 141). Packer suggests that the CR may “... play an increasingly important role in delivering care that fits the characteristics of the individual patient” (Packer, 2017b, p. 185).

Medical case reports will most probably stay with us as a necessary and inspiring genre often to be found in medical journals. However, it might be necessary to modify and adapt its format according to the changes in the field of medicine.

5. CONCLUSIONS

1. The various merits and limitations of the modern CR were extracted and elaborated. This information can assist the medical community in deliberating whether the CR is the optimal article type for disseminating clinical observations. If an assessment finds the merits outweighing the limitations, reporting the observed case seems warranted.

2. Bibliometric data: Quantification of empirical data on the particular elements of case reports can inform about the characteristics and current trends in the field of case reporting. We assume that this knowledge can be useful in guiding CR writers in choosing the appropriate article type, be it the case report or other study designs. As our study assessed some selected characteristics of CRs from a university hospital, it might be used by other hospitals or health centres as a benchmark for their own replication studies.

3. Three different case reports from the field of psychiatry highlight these issues:

- a) Physical restraint and potentially lethal asphyxia,
- b) Some of the side effects of clozapine medication,
- c) The existence of the rare disorder Clenched fist syndrome, and the dearth of publications about it in the psychiatric literature.

As the three CR articles are published and thus accessible to the readership, they represent a contribution to the medical scientific literature.

The CR is a central and vital medical genre, with a very long history in medicine. The CR has many merits that have further broadened its appeal today, but it also has some limitations that should be kept in mind. The CRs included in the thesis, as most modern CRs, share some similarities in their structure, but show much variability in their topics. While many CRs adhere to a strict biomedical approach, it is also possible to take a more biopsychosocial approach to CRs. The CR is likely to play an important part in medicine also in the future.

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7. APPENDIX

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<p>Milos Jenicek (1999) <i>Clinical case reporting in Evidence based medicine</i>. Oxford: Butterworth Heinemann</p>	<p>Milos Jenicek</p>	<p>February 2013</p>
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8. ARTICLES 1-5

Article 1

RESEARCH ARTICLE

Open Access

The clinical case report: a review of its merits and limitations

Trygve Nissen^{1,2} and Rolf Wynn^{1,3*}

Abstract

Background: The clinical case report has a long-standing tradition in the medical literature. While its scientific significance has become smaller as more advanced research methods have gained ground, case reports are still presented in many medical journals. Some scholars point to its limited value for medical progress, while others assert that the genre is undervalued. We aimed to present the various points of view regarding the merits and limitations of the case report genre. We searched Google Scholar, PubMed and select textbooks on epidemiology and medical research for articles and book-chapters discussing the merits and limitations of clinical case reports and case series.

Results: The major merits of case reporting were these: Detecting novelties, generating hypotheses, pharmacovigilance, high applicability when other research designs are not possible to carry out, allowing emphasis on the narrative aspect (in-depth understanding), and educational value. The major limitations were: Lack of ability to generalize, no possibility to establish cause-effect relationship, danger of over-interpretation, publication bias, retrospective design, and distraction of reader when focusing on the unusual.

Conclusions: Despite having lost its central role in medical literature in the 20th century, the genre still appears popular. It is a valuable part of the various research methods, especially since it complements other approaches. Furthermore, it also contributes in areas of medicine that are not specifically research-related, e.g. as an educational tool. Revision of the case report genre has been attempted in order to integrate the biomedical model with the narrative approach, but without significant success. The future prospects of the case report could possibly be in new applications of the genre, i.e. exclusive case report databases available online, and open access for clinicians and researchers.

Keywords: Case reports, Case series, Merits, Limitations, Methodology

Background

Throughout history the clinical case report and case report series have been integral components of medical literature [1]. The case report genre held a strong position until it was sidelined in the second half of the 20th century [2,3]. New methodologies for research articles paved the way for evidence-based medicine. Editors had to make space for these research articles and at the same time signaled less enthusiasm for publishing case reports [4]. This spurred some heated debates in medical journals as

readers were worried that the traditional case report was in jeopardy [5,6]. Those who welcomed the new trend with fewer case reports being published pointed mainly to their low quality and inclination to emphasize mere curiosity [7-9]. Some of the proponents of the genre claimed that the case report had been and still was indispensable for furthering medical knowledge and that it was unique in taking care of the detailed study of the individual patient as opposed to the new research methods with their "...nomothetic approach [taking] precedence..." [5]. Still, the case report got a low ranking on the evidence hierarchy. After a decline in popularity a new interest for the case report emerged, probably beginning in the late 1990s [2]. A peer-reviewed 'Case reports' section was introduced in the *Lancet* in 1995 [10]. In 2007, the first international, Pubmed-listed medical journal publishing only case

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reports was established [11,12]. In the following years, several similar journals, for the most part online and open-access, have been launched.

The present debate is not so much focused on whether case reporting is obsolete or not. Some of the discussions after the turn of the century have been about adapting the case report genre to new challenges. One example is the suggestion of incorporating the narrative, i.e. "... stressing the patient's story", in the case report [13]. The authors termed their initiative "The storied case report". Their endeavor was not met with success. In analyzing the causes for this, they wondered if "... junior trainees find it too hard to determine what is relevant and senior trainees find it too hard to change their habits" [13]. A similar attempt was done when the editors of the *Journal of Medical Case Reports* in 2012 encouraged authors to include the patients' perspectives by letting patients describe their own experiences [14].

Notwithstanding, we feel there is much to be gained from having an ongoing discussion highlighting the indications and contraindications for producing case reports. This can to some degree be facilitated by getting an understanding of the merits and limitations of the genre. The objective of this article is to present the merits and limitations of case reports and case series reports.

Methods

We adopted *Taber's Cyclopedic Medical Dictionary's* definition of the *case report*: "A formal summary of a unique patient and his or her illness, including the presenting signs and symptoms, diagnostic studies, treatment course and outcome" [15]. A case report consists of one or two cases, most often only one. The *case series* or *case series report* usually consists of three to ten cases [16]. (In the following we use the term case report to denote both case reports and case series report). Case reports are most often naturalistic and descriptive. Sometimes, however, they can be prospective and experimental.

As literature specifically dealing with the case report genre seemed harder to elicit from the databases than the vast amount of particular case reports, we performed iterative searches. We searched Google Scholar and PubMed using the search terms 'case report(s)', 'case series', 'case series report(s)', 'case reporting' in various combinations with 'clinical', 'medical', 'anecdotal', 'methodology', 'review', 'overview', 'strengths', 'weaknesses', 'merits', and 'limitations'. Further references were identified by examining the literature found in the electronic searches. We also consulted major textbooks on epidemiology [17,18], some scholars of medical genres [19,20] and a monograph on case reporting by the epidemiologist M. Jenicek [16]. We delimited our review to the retrospective, naturalistic, and descriptive case report, also labeled the "traditional" or "classic" case report, and case series including such

reports. Thus we excluded other types, such as the planned, qualitative case study approach [21] and simulated cases [22-24]. Finally, we extracted the relevant data and grouped the merits and limitations items in rank order with the items we judged to be the most important first.

Results

Merits

New observations

The major advantage of case reporting is probably its ability to detect novelties [16]. It is the only way to present unusual, uncontrolled observations regarding symptoms, clinical findings, course of illness, complications of interventions, associations of diseases, side effects of drugs, etc. In short, anything that is rare or has never been observed previously might be important for the medical community and ought to be published. A case report might sensitize readers and thus facilitate detection of similar or identical cases.

Generating hypotheses

From a single, or preferably several single case reports or a case series, new hypotheses could be formulated. These could then be tested with formal research methods that are designed to refute or confirm the hypotheses, i.e. comparative (observational and experimental) studies.

There are numerous examples of new discoveries or major advancements in medicine that started with a case report or, in some cases, as humbly as a letter to the editor. The first concern from the medical community about the devastating side effect of thalidomide, i.e. the congenital abnormalities, appeared as a letter to the editor in the *Lancet* in 1961 [25]. Soon thereafter, several case reports and case series reports were published in various journals. Case reporting is thus indispensable in drug safety surveillance (pharmacovigilance) [26].

Sometimes significant advancements in knowledge have come not from what researchers were pursuing, but from "accidental discoveries", i.e. by serendipity. The story of Alexander Fleming's discovery of penicillin in 1928 is well known in the medical field [27]. Psychiatry has profited to a large degree from this mode of advancing medical science as many of the drugs used for mental disorders have been discovered serendipitously [27]. One notable example is the discovery of the effect of lithium on manic episodes in patients with manic-depressive disorder [28]. A more recent discovery is the successful treatment of infantile hemangiomas with systemic propranolol. This discovery was published, as a case series report, in the correspondence section in *New England Journal of Medicine* [29]. However, the evidence for the effect of this treatment is still preliminary, and several randomized trials are under way [30,31].

Clear and operational entities are prerequisites for doing medical research. Descriptions must come before understanding. Clinical observations that lead to new disorders being described are well suited for case reporting. The medical literature is replete with case-based articles describing new diseases and syndromes. One notable example is the first description of neurasthenia by G. Beard in *Boston Medical and Surgical Journal* in 1869 [32].

Researching rare disorders

For rare disorders randomized controlled trials (RCTs) can be impossible to run due to lack of patients to be enrolled. Research on drug treatment and other kinds of interventions must therefore be based on less rigorous methodologies, among them case series and case reports. This would be in accordance with the European Commission's recommendation to its members to improve health care for those with rare disorders [33].

Solving ethical constraints

Case reporting can be valuable when ethical constraints prohibit experimental research. Take as an example the challenge of how to manage the side effects of accidental extravasation of cytotoxic drugs. As RCTs on humans seem unethical in this clinical situation the current guidelines rest on small observational studies, case reports and animal studies [34]. Or another example: Physical restraint is sometimes associated with sudden, unexpected death. The cause or causes for this are to some degree enigmatic, and it is hard to conceive of a controlled study that could be ethical [35,36]. Case reports and case series being "natural experiments" might be the only evidence available for guiding clinical practice.

In-depth narrative case studies

Case reporting can be a way of presenting research with an idiographic emphasis. As contrasted to nomothetic research, an idiographic approach aims at in-depth understanding of human phenomena, especially in the field of psychology and psychiatry. The objective is not generalizable knowledge, but an understanding of meaning and intentionality for an individual or individuals. Sigmund Freud's case studies are relevant examples. This usage of case reports borders on qualitative research. Qualitative studies, although developed in the social sciences, have become a welcome contribution within health sciences in the last two decades.

Educational value

Clinical medical learning is to a large degree case-based. Typical case histories and vignettes are often presented in textbooks, in lectures, etc. Unusual observations presented as published case reports are important as part of

doctors' continuing medical education, especially as they demonstrate the diversity of manifestations both within and between medical diseases and syndromes [37,38]. Among the various medical texts, the case report is the only one that presents day-to-day clinical practice, clinicians' diagnostic reasoning, disease management, and follow-up. We believe that some case reports that are written with the aim of contributing to medical knowledge turn out to be of most value educationally because the phenomena have already been described elsewhere. Other case reports are clearly primarily written for educational value [37]. Some journals have regular sections dedicated to educational case reports, e.g. The Case Records of the Massachusetts General Hospital in the *New England Journal of Medicine* and the Clinical Case Conference found in the *American Journal of Psychiatry*.

Expenses

The cost of doing a case report is low compared to planned, formal studies. Most often the necessary work is probably done in the clinical setting without specific funding. Larger studies, for instance RCTs, will usually need an academic setting.

Fast publication

The time span from observation to publication can be much shorter than for other kinds of studies. This is obviously a great advantage as a case report can be an important alert to the medical community about a serious event. The unexpected side effects of the sedative-antinauseant thalidomide on newborn babies is a telling story. The drug had been prescribed during pregnancy to the babies' mothers. After the first published observation of severe abnormalities in babies appeared as a letter to the editor of the *Lancet* in December 16th, 1961 [25], several case reports and series followed [39,40]. It should be mentioned though that the drug company had announced on December 2nd, 1961, i.e. two weeks before the letter from McBride [25], that it would withdraw the drug from the market immediately [41].

Flexible structure

Riaz Agha, editor of the *International Journal of Surgery Case Reports* suggests that the case report, with its less rigid structure is useful as it "... allows the surgeon(s) to discuss their diagnostic approach, the context, background, decision-making, reasoning and outcomes" [42]. Although the editor is commenting on the surgical case report, the argument can be applied for the whole field of clinical medicine. It should be mentioned though, that other commentators have argued for a more standardized, in effect more rigid, structure [43].

Clinical practice can be changed

Case reporting can lead to or contribute to a change in clinical practice. A drug might be withdrawn from the market. Or a relabeling might change the attitude to and treatment of a condition. During World War I the shell shock syndrome was labeled and described thoroughly in several articles in the *Lancet*, the first of them appearing in February 1915 [44]. The author was the British captain and military doctor Charles S. Myers. Before his efforts to bring good care and treatment to afflicted soldiers there had been a common misconception that many of these dysfunctional soldiers were malingerers or cowards.

Exercise for novice researchers

The case report format is well suited for young doctors not yet trained as researchers. It can be an opportunity for a first exercise in authoring an article and a preparation for a scientific career [37,45,46].

Communication between the clinical and academic fields

Articles authored by clinicians can promote communication between practicing clinicians and academic researchers. Observations published can generate ideas and be a trigger for further studies. For instance, a case series consisting of several similar cases in a short period can make up the case-group for a case-control study [47]. Clinicians could do the observation and publish the case series while the case-control study could be left to the academics.

Entertainment

Some commentators find reading case reports fun. Although a rather weak argument in favor of case reporting, the value of being entertained should not be dismissed altogether. It might inspire physicians to spend more time browsing and reading scientific literature [48].

Studying the history of medicine

Finally, we present a note on a different and unintended aspect of the genre. The accumulated case reports from past eras are a rich resource for researching and understanding medical history [49,50]. A close study of old case reports can provide valuable information about how medicine has been practiced through the centuries [50,51].

Limitations

No epidemiological quantities

As case reports are not chosen from representative population samples they cannot generate information on rates, ratios, incidences or prevalences. The case or cases being the numerator in the equation, has no denominator. However, if a case series report consists of a cluster of cases, it can signal an important and possibly

causal association, e.g. an epidemic or a side effect of a newly marketed drug.

Causal inference not possible

Causality cannot be inferred from an uncontrolled observation. An association does not imply a cause-effect relationship. The observation or event in question could be a mere coincidence. This is a limitation shared by all the descriptive studies [47]. Take the thalidomide tragedy already mentioned as an example; Unusual events such as congenital malformations in some of the children born to mothers having taken a specific drug during pregnancy does not prove that the drug is the culprit. It is a mere hypothesis until further studies have either rejected or confirmed it. Cause-effect relationships require planned studies including control groups that to the extent possible control for chance, bias and confounders [52].

Generalization not possible

From the argument above, it follows that findings from case reports cannot be generalized. In order to generalize we need both a cause-effect relationship and a representative population for which the findings are valid. A single case report has neither. A case series, on the other hand, e.g. many “thalidomide babies” in a short time period, could strengthen the suspicion of a causal relationship, demanding further surveillance and research.

Bias

Publication bias could be a limiting factor. Journals in general favor positive-outcome findings [53]. One group of investigators studying case reports published in the *Lancet* found that only 5% of case reports and 10% of case series reported treatment failures [54]. A study of 435 case reports from the field of dentistry found that in 99.1%, the reports “...clearly [had] a positive outcome and the intervention was considered and described as successful by the authors” [55].

Overinterpretation

Overinterpretation or misinterpretation is the tendency or temptation to generalize when there is no justification for it. It has also been labeled “the anecdotal fallacy” [56]. This is not a shortcoming intrinsic to the method itself. Overinterpretation may be due to the phenomenon of case reports often having an emotional appeal on readers. The story implicitly makes a claim to truth. The reader might conclude prematurely that there is a causal connection. The phenomenon might be more clearly illustrated by the impact of the clinician’s load of personal cases on his or her practice. Here exemplified by a young doctor’s confession: “I often tell

residents and medical students, “The only thing that actually changes practice is adverse anecdote.” [57].

Emphasis on the rare

As case reporting often deals with the rare and atypical, it might divert the readers’ attention from common diseases and problems [58].

Confidentiality

Journals today require written informed consent from patients before publishing case reports. Both authors and publishers are responsible for securing confidentiality. A guarantee for full confidentiality is not always possible. Despite all possible measures taken to preserve confidentiality, sometimes the patient will be recognized by someone. This information should be given to the patient. An adequately informed patient might not consent to publication. In 1995 in an Editorial in the *British Journal of Psychiatry* one commentator, Isaac Marks, feared that written consent would discourage case reports being written [59]. Fortunately, judged from the large number of reports being published today, it seems unlikely that the demand for consent has impeded their publication.

Other methodological limitations

Case reports and series are written after the relevant event, i.e. the observation. Thus, the reports are produced retrospectively. The medical record might not contain all relevant data. Recall bias might prevent us from getting the necessary information from the patient or other informants such as family members and health professionals.

It has also been held against case reporting that it is subjective. The observer’s subjectivity might bias the quality and interpretation of the observation (i.e. information bias).

Finally, the falsification criterion within science, which is tested by repeating an experiment, cannot be applied for case reports. We cannot design another identical and uncontrolled observation. However, unplanned similar “experiments” of nature can be repeated. Several such observations can constitute a case series that represents stronger indicative evidence than the single case report.

Discussion

The major advantages of case reporting are the ability to make new observations, generate hypotheses, accumulate scientific data about rare disorders, do in-depth narrative studies, and serve as a major educational tool. The method is deficient mainly in being unable to deliver quantitative data. Nor can it prove cause-effect relationship or allow generalizations. Furthermore, there is a risk of overinterpretation and publication bias.

The traditional case report does not fit easily into the qualitative-quantitative dichotomy of research methods. It certainly shares some characteristics with qualitative research [16], especially with regard to the idiographic, narrative perspective – the patient’s “interior world” [60] – that sometimes is attended to. Apart from “The storied case report” mentioned in the Background-section, other innovative modifications of the traditional case report have been tried: the “evidence-based case report” [61], the “interactive case report” [62] and the “integrated narrative and evidence based case report” [63]. These modifications of the format have not made a lasting impact on the way case reports in general are written today.

The method of case reporting is briefly dealt with in some textbooks on epidemiology [17,18]. Journals that welcome case reports often put more emphasis on style and design than on content in their ‘instruction to authors’ section [64]. As a consequence, Sorinola and co-workers argue for more consensus and more consistent guidance on writing case reports [64]. We feel that a satisfactory amount of guidance concerning both style and content now exists [12,16,65,66]. The latest contribution, “The CARE guidelines”, is an ambitious endeavor to improve completeness and transparency of reports [66]. These guidelines have included the “Patient perspective” as an item, apparently a bit half-heartedly as this item is placed after the Discussion section, thus not allowing this perspective to influence the Discussion and/or Conclusion section. We assume this is symptomatic of medicine’s problem with integrating the biomedical model with “narrative-based medicine”.

In recent years the medical community has taken an increased interest in case reports [2], especially after the surge of online, exclusive case report journals started in 2007 with the *Journal of Medical Case Reports* (which was the first international, Pubmed-listed medical journal publishing only case reports) as the first of this new brand. The climate of skepticism has been replaced by enthusiasm and demand for more case reports. A registry for case reports, Cases Database, was founded in 2012 [67]. On the condition that it succeeds in becoming a large, international database it could serve as a register being useful for clinicians at work as well as for medical research on various clinical issues. Assuming Pamela P. Powell’s assertion that “[a]lmost all practicing physicians eventually will encounter a case worthy of being reported” [60] is valid, there should be no shortage of potential cases waiting to be reported and filed in various databases, preferably online and open access.

Limitations of this review

There are several limitations to this study. It is a weakness that we have not been able to review all the relevant literature. The number of publications in some way

related to case reports and case report series is enormous, and although we have attempted to identify those publications relevant for our purpose (i.e. those that describe the merits and limitations of the case report genre), we might have missed some. It was difficult to find good search terms for our objective. Still, after repeated electronic searches supplemented with manual searches in reference lists, we had a corpus of literature where essentially no new merits or limitations emerged.

As we point out above, the ranking of merits and limitations represents our subjective opinion and we acknowledge that others might rank the importance of the items differently.

The perspective on merits and limitations of case reporting has been strictly medical. As a consequence we have not analyzed or discussed the various non-medical factors affecting the publication of case reports in different medical journals [2]. For instance, case reports are cited less often than other kinds of medical research articles [68]. Thus they can lower a journal's impact factor, potentially making the journal less attractive. This might lead some high-impact journals to publish few or no case reports, while other journals have chosen to specialize in this genre.

Conclusions

Before deciding on producing a case report or case series based on a particular patient or patients at hand, the observant clinician has to determine if the case report method is the appropriate article type. This review could hopefully assist in that judgment and perhaps be a stimulus to the continuing debate in the medical community on the value of case reporting.

Competing interests

The authors declare that there are no competing interests.

Authors' contributions

TN contributed to the conception, drafting, and revision of the article. RW contributed to the conception, drafting, and revision of the article. Both authors approved the final manuscript.

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Article 2

ARTICLE

The case of case reports: a decade of publications by staff at a major university hospital

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Abstract

Rationale: The place of case reports in the medical literature has been much debated in recent years. This study was undertaken to gain knowledge about the publication practice of case reports and case series from a major university hospital.

Method: We decided to conduct a retrospective, bibliographic, descriptive study of published case reports and case series from a university hospital in a period of 10 years. The following variables were studied: number of reports, authorship characteristics, collaboration practices, titles, medical specialities represented, educational *versus* non-educational purpose and number of citations. The data were extracted from the national research information system database in Norway.

Results: 2.2% of all the publications were case reports. Multiple authorship was common. Male authors outnumbered female authors. Collaboration across hospitals and nations occurred for one third of the articles. 43% of the titles did not contain information that identified them as case reports or case series. The most frequently represented specialties were neurology, rheumatology, plastic surgery and medical genetics. Nine out of 10 articles were non-educational. A third of the articles had not been cited.

Conclusions: The case report seems to be a minor, although viable, genre. The proportion of case reports and case series was low. A plausible hypothesis could be that clinician-researchers at the study hospital prioritized controlled clinical and paraclinical/laboratory studies that rank higher on the evidence hierarchy. Since case reports document the presentations of individual patients and their treatment, a declining interest in their publication has a significant implication for person-centered healthcare education and training.

Keywords

Authorship, bibliometric case reports, citations, collaboration practices, medical specialities, person-centered healthcare, titles

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Introduction

Medical writing has been the object of interest and study among medical researchers and scholars of writing studies, literature and linguistics [1-5]. Among the various medical genres, the clinical case report is probably the oldest [6]. Egyptian papyri dating from the 16th-17th Dynasty, that is, 1650-1550 B.C., contain case reports with an emphasis on treatment [7]. These were typical cases, not individual ones, instructing on diagnosis and treatment. The linguist Dwight Atkinson found single cases of disease to be the most common article type in the *Edinburgh Medical Journal* in the 18th Century [4]. In a study of publications from three general medical journals - the *Journal of the American Medical Association*, the

Lancet and the *New England Journal of Medicine* - in the period from 1946-1976, case reports and case series comprised 38% of the articles [8]. The authors defined "case report" as including 10 or fewer patients. Thirteen percent were single case reports. There was no significant decline in this period. The reduction, both in number and proportion, of case reports and case series came later. In the period from 1971 to 1991 there was a reduction from 30% to 4% case reports in the same three journals [9]. In the 1980s, the proportion of the articles fell from 17.4% to 2.4% in the *American Journal of Psychiatry* and the *Archives of General Psychiatry* [10].

The percentage of case reports and case series declined from 19% in 1991 to 1% in 2001 in the journal *Obstetrics & Gynecology* [11]. The trend towards decreasing number of case reports was not ubiquitous,

however. Some journals kept the number of case reports at fairly steady levels, 34-45% and 13% respectively in two studies, from around 1980 to the late 1990s [1,12]. Anyhow, the case report genre plays a minor role in most medical journals today [13,14].

Other areas of interest concerning case reporting have been medical specialty, authorship, collaboration practices, citations, titles and 'instruction to authors' [3,15-18]. The source of data for these studies has usually been limited to one or a few medical journals and the results may thus reflect editorial policies or other unique aspects of these specific journals. We do not know of any previous studies that have focused on the output of case reports from a university hospital. Knowledge about various quantitative characteristics of case reports might inform us about developments and trends in medical practice and research, including editorial policies in general and their significance for person-centered healthcare education and training.

The objective of this study was to explore the publication practice among professionals at a university hospital with regard to case reports and case series, focusing on the following variables: 1) The production of case reports and case series, 2) Issues related to authorship (number of authors per article, gender distribution, gender of first and last author), 3) Collaborative practices (local, national, international), 4) Titles, 5) Medical specialities represented, 6), Educational or non-educational purpose and 7) The number of citations.

Methods

We decided to conduct a retrospective, bibliographic, descriptive study of published case reports and case series from the University Hospital of North Norway which we subsequently term *the study hospital*. We applied *Taber's Cyclopedic Medical Dictionary's* definition of case report, "A formal study of a unique patient and his or her illness, presenting signs and symptoms, diagnostic studies, treatment course and outcome" [19], although with the modification that we allowed for 2 cases in the report. Articles based on hypothetical or simulated cases or case series were excluded [20-22]. A case series or case series report was operationalised as 3-12 cases in this study. Inclusion criteria were: All case report articles, case series articles and case reports-abstracts published in peer-reviewed medical journals, national or international and registered in the Current Research Information System in Norway (abbreviated CRISStin) for the 10-year period 2004-2013 [23]. At least one of the authors had to be employed at the University Hospital of North Norway.

All the articles published in scientific journals by employees of the hospital during the study period were screened for research design. Searching the database allowed for reviewing every article in a stepwise manner. The first step was inspecting the particular article for authorship, title and journal reference. Step two allowed access to the abstract and full text article. Thus, we could

determine research design for all articles. This procedure made for a full catch of all case reports and case series in the CRISStin database for the 10-year period. The number in the database deviates somewhat from the total number of articles produced by the hospital researchers. The database stores only articles that are actively reported by those who have written them. There will be some articles missing, especially in the early years of the period as the current incentives for having articles in the database (e.g., the possibility of receiving financial support, being privileged sabbaticals for those also having university affiliations, *etc.*) were not implemented at that time. Therefore, our material refers only to the corpus of articles found in the database and not the complete number of articles published in the period. The discrepancy between the real and the assembled number is unknown, but we suggest that it is likely to be quite low.

Following identification of all articles, the following data were extracted: (a) The number of case reports and case series, respectively; (b) the number of male and female authors; (c) the gender of the first and last author; (d) the number of articles with local, national and international authorship; (e) whether the title was identifiable or not; (f) the article's primary medical specialty; (g) whether the article had an educational or non-educational aim and (h) the number of citations. The first author is usually the one who has contributed the most to the work. The last author position is usually reserved for the senior author and/or supervisor.

Definitions

The authorship was characterized as *local* if all the authors worked at the study hospital. *National authorship* required authors at two or more institutions in different locations in Norway, with at least one author from the study hospital. If at least one of the authors was working in another country at the time of writing the article, we defined it as *international authorship*. These categories are essentially identical to those of Salager-Meyer and co-workers [3].

A title was labelled *identifiable* if it unequivocally identified an article as a case report or case series, as seen in these two titles:

Progressive multifocal leucoencephalopathy in an immunocompetent patient with favourable outcome. A case report.

Imported case of visceral leishmaniasis presenting in a Norwegian patient treated with methotrexate and etanercept for psoriasis arthritis.

Most titles in the CRISStin database other than case reports were relatively easily excluded when the title contained information on study design, for example, *Chemoradiotherapy of anal carcinoma: Survival and recurrence in an unselected national cohort*. A national cohort is obviously not a case report. Ambiguous article titles had to be meticulously looked into, either by

studying the abstract or the full text version. These are three examples of titles that we discovered to be case reports:

Focal myositis – Aneurogenic phenomenon?

A Little bleed

Arctic environment triggers migraine attacks.

The ambiguous titles were labeled *non-identifiable* as the title itself was not conclusive as to the articles' design or type of study.

Specialty areas for the case reports were identified by the hospital department affiliation (e.g., Gastrointestinal Surgery, Neurology) of the authors. In the case of authors from different departments, we determined specialty according to the first author's specialty affiliation and/or which primary organ system that was described in the text.

Some medical journals, for example, the *New England Journal of Medicine*, the *Lancet*, the *Journal of the Norwegian Medical Association*, have devoted space for regular case reports with an educational aim. These are often supplemented with a commentary by one or several senior specialists. We labelled reports in this category *educational case reports* so as to differentiate them from articles with an ambition of presenting new findings or otherwise further medical knowledge. The last mentioned type was labeled *non-educational*. The number of *citations* for all articles were found by searching the Google Scholar database.

Results

The study material

In total, 2313 published articles from the study hospital were found in the CRISTin database for the 10-year period. Fifty-one were case reports and series (2.2 % of the total number). (Table 1). Forty-one of these were case reports (80%) and 10 were case series (20%).

Table 1 Types of case reports included

Article type	No (%)
Case reports	41 (80)
With 1 case	36 (70)
With 2 cases	5 (10)
Case series	10 (20)

The total number of cases in the 10 case series was 55, giving a mean of 5.5, median 4, mode 3, range 3-12.

Authorship

The total number of authors of the 51 articles was 226. The average number of authors per article was 4.4, with a range of 1-24. If we omit the one outlier article with 24 authors, the mean would be 4.0. The distribution was skewed to the right, both mode and median values were 3. The gender distribution is presented in Table 2.

Table 2 Gender and authorship position of case reports

Gender	All authors No. (%)	First author No. (%)	Last author No. (%)
Women	67 (30)	13 (25)	9 (18)
Men	159 (70)	38 (75)	42 (82)
Total	226 (100)	51 (100)	51 (100)

Table 3 Collaboration practices in case reports

Level	No (%)
Local	33 (65)
National	11 (22)
International	7 (14)
Total	51 (101)*

*Percentage higher than 100 due to rounding errors on individual percentages in the column above.

Article titles

Twenty-nine articles (57%) contained sufficient information to be identified as case reports leaving 22 (43%) without identifier as to type of study design.

Medical specialty

Table 4 Contribution of case reports from the different medical specialties

Medical specialty	No. of reports (%)
Neurology	9 (17.6)
Rheumatology	8 (15.7)
Plastic surgery	5 (9.8)
Medical genetics	5 (9.8)
Anesthesia / emergency medicine	4 (7.8)
Hematology	3 (5.9)
Infectious medicine	2 (3.9)
Clinical pharmacology	2 (3.9)
Pathology	2 (3.9)
Psychiatry	2 (3.9)
Abdominal surgery	2 (3.9)
Physiotherapy	1 (2.0)
Pediatrics	1 (2.0)
Rehabilitation & physical medicine	1 (2.0)
Medical biochemistry	1 (2.0)
Urological surgery	1 (2.0)
Cardiothoracic surgery	1 (2.0)
Oncology	1 (2.0)

Forty-one reports/series (80.4%) were clinical and 10 (19.6%) were paraclinical (pathology, clinical pharmacology, medical biochemistry, medical genetics). Nine (18% of the total number) of the clinical reports/series were surgical, whereas 32 (63%) were non-surgical.

Educational versus non-educational

Six case reports (12%) were educational, 45 (88%) were non-educational.

Citations

Table 5 Number of citations per case report

No. of citations	No. of articles (%)
0	17 (33.3)
1	11 (21.6)
2	5 (9.8)
3	2 (3.9)
4	3 (5.9)
5	3 (5.9)
6	1 (2.0)
8	1 (2.0)
10	2 (3.9)
11	1 (2.0)
12	1 (2.0)
15	2 (3.9)
18	1 (2.0)
45	1 (2.0)

One third of the articles had not been cited. The mean number of citations per article was 4.0. The median was 1.

Discussion

Case reports

The percentage of case reports from our hospital (2.2%) is yet another indication that the case report has lost its central position in the medical literature [13,14]. As already mentioned, we do not have data from other hospitals for comparison. Therefore, we abstain from passing any judgement as to whether the percentage should be higher or lower. However, we find it interesting that 13% of all articles in the *Australian and New Zealand Journal of Psychiatry* in the 33-year period 1976-1999 were case reports [1]. The authors, after having discussed the advantages and shortcomings of the case report, suggested that the genre should still be retained as full articles in the journal, "... but perhaps

account for less than 13%." Furthermore, as our study was descriptive with a relatively short time span, a low number of reports and some uncertainty about the number of missing reports, we cannot identify any clear temporal trend.

Authorship

The mean number of authors per article was 4.4, the median was 3. This is in line with previous research on case reports [3,24-26]. This is somewhat lower than for research articles with more advanced methodologies [9,26,27]. Only one case report in our corpus had a single author. The trend the last decades has been an increasing number of authors in medical articles in general [9,26,27]. This is partly explained by medicine having become more complex and dependent on team work [9,26], although the phenomenon of honorary or gift authorship might explain some cases of multiple authorships [28,29]. Our study was not designed to reveal whether honorary authorships were prevalent, but we admit being surprised when finding one article with 24 authors. The rhetorical question: "Does it take a village to write a case report?" by Gady Har-El in *Otolaryngologia - Head and Neck Surgery*, seems apposite [29].

As concerns gender distribution, there was a male dominance with a male to female ratio of 7:3 for all authors and somewhat larger imbalances for the first and last author (Table 2). We take this as a corroboration of the findings of other investigators [30,31]. Gender authorship appears to be a valid surrogate marker of the gender imbalance of medical publishing [30]. Among doctors and psychologists (who do most of the research at the study hospital), there were in 2005 59% males and 41% females [32]. As the ratio between the sexes has been equalizing in the years following 2005, we feel justified in assuming that male doctors are somewhat more given to writing case reports than female doctors at the study hospital.

Collaboration practices

During the last decades, a growth in collaboration practices has taken place [33]. A study from Taiwan investigated the country's clinical medical articles indexed in the Institute for Scientific Information (ISI) database (ISI Essential Science Indicators) from the period 1990-2004 [34]. A total of 13.6% of the clinical medical articles were produced with an international collaboration. A Malaysian study found local collaboration accounting for 60.3% and international collaboration for 39.7% of clinical medical articles [35]. Salager-Meyer and co-workers investigated exclusively case reports in their diachronic study of the *British Medical Journal* and *BMJ Case Reports* [3]. For the year 2009, they found that 68.3% of case reports were written by authors from the same city (local collaboration), 26.7% had national authorship while only 1.6% were the result of international collaboration. In our hospital-based study the corresponding numbers were 65%, 22% and

14%. Both Salager-Meier's study and ours had lower rates for international collaboration than the two Asian studies referred to above. This should not come as a surprise as case reports usually require less resources and co-operation than larger and more elaborately designed studies. What really was surprising, however, was the number of single-authored case reports. All the 60 case reports published in the 1840-1850 corpus were single-authored, while this was the case with only 2, that is, 3.3%, in 2009 [3]. In our study, only one case report (2%) was written by a single author.

Article titles

Almost half of the titles (43%) did not suggest that the articles were case reports or case series. This was surprising considering the increasing emphasis on the function of titles as identifiers in bibliographic information retrieval systems [17]. The *Journal of Medical Case Reports* instructs authors to include a study design specifier, either "a case report" or "a case series", in the title [36]. The journal suggests this format for the title: *A presenting with B in C: a case report*. This is an example: *Clinical picture and treatment implication in a child with Capgras syndrome: a case report* [37].

Medical specialty

According to the relative "size" (i.e., clinical importance in terms of number of patients treated, number of specialists, etc.) of the various specialties, some appear to be over-represented (neurology, rheumatology, plastic surgery), some under-represented (psychiatry, oncology) and some missing (e.g., gastroenterology, cardiology, ophthalmology, otorhinolaryngology). The regular column named *Lancet Case Report* has been discussed twice in the *Lancet*. In 2003, three neurologists reviewed all the journal's case reports from 1996 to 2002 [38]. They found that the neurological organ system was disproportionately often presented (29%). It ranked high above the second one, which was gastroenterology with 15%.

At the lower end were psychiatry (2%) and ophthalmology (1%). Seven years later, neurology was still the dominant organ system represented in case report publications, but not to the same degree [15]. For the period 2003-2008, neurology accounted for 15% of case reports. Coles *et al.* suggested the dominance of neurology could be explained by "... the trepidation and interest that neurological syndromes generate among physicians" [38]. A review of the first 100 cases in the *Journal of Medical Case Reports*, a journal established in 2007, found general surgery and general medicine representing 11 each, followed by oncology (7), orthopaedics (7) and ophthalmology with 6 reports [39]. Only one report was neurological.

It seems wise not to put too much emphasis on the various proportions of medical disciplines being reported. A published case report is contingent on many factors: rare occurrence; observant and trained clinicians;

opportunity, willingness and time to collaborate with colleagues in order to produce a draft for an article; etc. [14].

From the study hospital we assume there were no obsolete reports. The high number of reports from neurology, rheumatology and plastic surgery can probably be ascribed to a few enthusiastic and very skilled clinicians in these specialties. It may also reflect different attitudes in the various specialties to the acceptance of writing and communicating patient cases. Furthermore, we might assume there have been some reportable cases that have not materialized as case reports. It is a well-known fact that many busy clinicians have little time for academic work.

Educational or non-educational purpose

A study of the characteristics of case reports published in a Danish general medical journal, *Ugeskrift for Læger* (*Weekly journal for doctors*), found that 124 of 140 reports (89%) had an educational purpose [24]. The main audience of this journal is Danish doctors. It is written in Danish, but articles are supplemented with a brief English summary. The authors assumed that the non-educational articles (e.g., discoveries of new associations) probably would be published in high-impact international journals, leaving the educational ones aimed for Danish readers for publication in the national Danish-language journal (*Ugeskrift for Læger*).

In our study, the proportions of educational and non-educational reports were the reverse. A plausible interpretation could be that clinicians at the study hospital find it more imperative and possibly more rewarding to share non-educational case reports with the medical community.

Citations

Citations of articles registered in the Web of Science allow for calculation of the impact factor of journals and articles. Few citations result in a low impact factor. Although the frequency of citations as a measure of quality and impact is debatable, it is essential in determining the prestige of health sciences journals [16,40]. Among the various study designs in health sciences, the case report seems to have a negligible citation impact [16]. Patsopoulos *et al.* documented a median of 1 citation count per article within the first two years of publication of case reports. Furthermore, less than 1% received more than 10 citations within the same time span. This contrasts with meta-analyses, the highest-ranking study design, for which 32.4% (in 1991) and 43.6% (in 2001) received more than 10 citations.

One third of the articles in our material were not cited. The average number of citations per article was 4.0. As the distribution was skewed, a more appropriate measure of the central tendency is the median, which was 1. Seven articles (14%) received more than 10 citations. A head on comparison with the study of Patsopoulos *et al.* is inappropriate considering the different

methodologies. Some of the articles in our material had a 10-year period to accumulate citations while the basis for indexing in the Web of Science is only the first two years after publication. Furthermore, there appears to be a trend in recent years towards higher citation rates that can partly be explained by the increasing number of journals worldwide [16].

A strength of this study was its innovativeness in which a university hospital was chosen as study object. We have not found any similar studies focusing on the output of cases from this type of institution. The quantitative data from this study could represent a benchmark for similar bibliometric studies from other hospitals, medical centers or health trusts. There are, however, several limitations to this study. The number of case-articles was relatively modest despite reviewing a 10-year period of publications. We had no good comparison studies, that is, similar studies from other hospitals or health trusts. Our source of articles, the CRISTin database [23], might not include all the published articles from the study hospital and some reports or case series might therefore be missing. Comparing our findings to the publication policies of individual journals is far from optimal. Still we feel this comparison could be justified as it helped us make some tentative interpretations.

Conclusions

Case reports and case series cannot be planned in the same way as experimental, elaborately designed research can. The production of a case report is thus contingent on a chance occurrence as well as diligent, observant and responsible clinicians undertaking the cumbersome work of producing the case report. In addition there has to be a health science journal willing to review and publish the report. Therefore, the total number of case reports from our study hospital does not allow for any clear conclusions. The proportion of 2.2% among all study designs could be a reflection of the genre's presently rather low status in medical literature. Multiple authorship was common and male authors outnumbered female authors. Collaboration across hospitals and nations occurred for one third of the articles, a significant number considering the lesser need for collaboration of this genre compared with other study designs. A relatively large proportion of titles did not inform adequately about the articles being case reports or case series. Of the medical specialties, neurology, rheumatology, plastic surgery and medical genetics stood out as the most productive, with more than half of the articles. Almost nine out of ten reports were non-educational. The uncitedness rate was close to one third.

Considering that only one in fifty articles was a case report or case series, a plausible hypothesis is that researchers at the study hospital prioritize other kinds of clinical and paraclinical/laboratory research, that is, controlled studies with research designs with a higher ranking on the evidence hierarchy. Since case reports

document the presentation of individual patients and their treatment, a declining interest in their publication has a significant implication for person-centered healthcare education and training.

Conflicts of Interest

The authors declare no conflicts of interest.

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Article 3

CASE REPORT**PSYCHIATRY & BEHAVIORAL SCIENCES**

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Physical Restraint and Near Death of a Psychiatric Patient

ABSTRACT: Physical restraint is used as a last resort emergency measure to calm and safeguard agitated and/or aggressive psychiatric patients. This can sometimes cause injuries, and rare fatalities have occurred. One mechanism of injury and death while in physical restraint is that of severe asphyxiation. We present the case of a hospitalized man in his mid-30s, suffering from schizophrenia. The patient was obese. He became aggressive and had to be manually restrained with a “takedown.” After having been put in the prone position on the floor with a significant weight load on his body, he lost respiration and consciousness. Subsequently, he was given CPR. He regained consciousness and respiration, while the cyanosis receded in 1–2 min. Psychiatrists and pathologists should be aware that physically restraining a patient in the prone position with a significant weight load on the torso can, in rare cases, lead to asphyxiation.

KEYWORDS: forensic science, forensic psychiatry, physical restraint, prone position, asphyxiation, schizophrenia

Physical restraint is an emergency measure that sometimes has to be resorted to in order to calm and safeguard an agitated or aggressive patient (1,2). This intervention can have adverse psychological and potentially deleterious physical effects (3,4). The most tragic outcome is the death of the patient (1–3). The suggested mechanism is thought to be asphyxiation (5,6). This is described in the literature variously as restraint asphyxia, mechanical asphyxia, positional asphyxia, and postural asphyxia (7,8). Some have disputed the concept of “positional asphyxia” and argue that factors other than body positioning appear to be more probable determinants for sudden deaths in persons in the prone “hogtie” custody restraint position (9–11). Among the factors that have been suggested to be more important are: illicit drug use, physiological stress, hyperactivity, hyperthermia, catecholamine hyperstimulation, and trauma from struggle.

We present a restraint episode in a psychiatric patient that came close to a fatal end and where the survival of the patient has resulted in information that could shed new light on the topic of asphyxiation during restraint.

The study was approved by the Hospital’s Data Protection Officer and by the Director of the Division of Addiction and Specialized Psychiatry. Written informed voluntary consent was obtained from the patient for publication of this case report.

Case Report

A Caucasian man, in his mid-30s, with a diagnosis of paranoid schizophrenia was being treated at a medium security unit at a

Norwegian University Hospital. From his teens, he had abused various illegal drugs, including amphetamine, cocaine, cannabis, lysergic acid diethylamide, ecstasy (MDMA or 3,4-methylenedioxymethamphetamine), anabolic steroids, and alcohol. He ended school prematurely in order to commit himself to the martial arts and had become proficient. He first came to psychiatric treatment 6 years before the reported incident. The last few years he had gained substantial weight, now being 120 kg. His body mass index was 42. The abdomen was large and protruding. He had dyspepsia and possibly bronchial asthma. The last few months before the incident, his psychotic condition gradually deteriorated. He had persecutory delusions, visual and auditory hallucinations, and anxiety. The regular medication was clozapine 600 mg/day (200 + 400 mg), chlorpromazine 100 mg TID, escitalopram 20 mg QD. On an “as needed” basis he used chlorpromazine 50–100 mg p.r.n. (max 300 mg per day), levomepromazine mixture 100 mg p.r.n. (max 200 mg per day), esomeprazole 20 mg p.r.n., and ipratropium bromide inhalation aerosol 20 µg/dose, 1–2 inhalations maximum three times per day.

Several attempts to reverse his psychotic decompensation, both psychopharmacologically and with regard to the milieu interventions, failed. At the time of the incident, he was in a severe psychotic state with visual and auditory hallucinations, persecutory delusions, anxiety, restlessness, agitation, and thought blocking. Having delusional ideas about another patient in the unit, he walked into this patient’s room in an aggressive and combative state. The staff at the unit immediately intervened whereupon a struggle started. Owing to the patient’s physical strength and vigorous struggling, the “takedown” turned out to be extremely difficult requiring at least 10 persons to keep him under control. The patient had to be placed in the prone “spread-eagle” fashion on the floor in order to prevent harm to others. A member of staff was supporting the patient’s head rotated to the side while simultaneously talking to him and observing his level of consciousness. Two persons held each of his arms and legs, and two had to lie with almost full body weight (about 80 kg

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each) on his torso. After about 2 min from the start of the “take-down,” staff noticed facial cyanosis, arrested respiration, and loss of consciousness, and spontaneous urination. Immediately, the restraint was released. He was turned around and placed in the supine position. CPR, that is, external cardiac massage and mouth-to-mouth breathing was started whereupon the patient after 1–2 min regained consciousness and respiration. The facial cyanosis was gradually replaced with normal skin color. There was a scant amount of vomit on his face. The episode lasted around 3–4 min from being put in the prone position until he had resumed respiration and normal skin color. In the turmoil, staff did not examine the peripheral pulse. The patient was now placed in recovery position, given oxygen on a mask, and pads for a heart-starter were attached to his chest. After about 10 min, paramedics arrived. Examination revealed the patient to be awake but obtunded, respiration was superficial (respiration rate 24 breaths/min). The skin was dry and warm. According to the registration on the heart-starter, the patient had sinus tachycardia with a heart rate of 120/min. The circulation was stable. Auscultation of lungs and heart was normal. Oxygen saturation measured with pulse oximetry in the ambulance was 94%. The patient was brought to the Cardiology Department for further observation and treatment. On arrival, his blood pressure was 140/85 mmHg. The peripheral pulse rate was regular, 110/min. The oxygen saturation was now 95%. ECG showed a sinus rhythm with heart rate 113/min, that is, sinus tachycardia. The QTc interval was 415 msec (normal < 440 msec). Chest X-ray was normal. Blood tests did not give any indication of myocardial infarction or any other physical disease. Blood-lactate was 2.4 mM (normal range 0.7–1.8 mM) indicating hyperlactatemia. Serum clozapine was 2870 nM (estimated normal range 300–2500 nM). The total amount of chlorpromazine equivalents (12 administered the last 24 h, regular and on demand, was 1500 mg. He had an uneventful recovery and was readmitted to the Psychiatric Department the next day. He suffered no physical sequelae.

When interviewed later, the patient said that he could recall all events up to the moment immediately before losing consciousness and, after that, he remembered being transported in the ambulance. He could also recall that while being restrained he had difficulty in breathing and think he said, “I can’t breathe” to the restrainers. The staff taking part in the restraining could not recall hearing this, however. Curiously, the patient denied being afraid or panicking during the episode. A thorough review of his medical history could not substantiate the suspect bronchial asthma. In retrospect, an alternative explanation for his occasional subjective respiratory problems could be anxiety, a symptom that is sometimes wrongly diagnosed as asthma.

Discussion

We have presented a case where the patient was physically restrained in the prone position, with a heavy weight load on his back, and where he subsequently lost respiration and consciousness. The suggestion that the prone position in some circumstances can interfere with respiration causing asphyxia and even death is not new (5,13,14). The term *restraint asphyxiation* was first proposed in 1993 by O’Halloran and Lewman (6). It expanded the concept of positional asphyxia to include the process of subduing and either physically or mechanically restraining an individual and was later suggested reserved for “...deaths during restraint that appear to be the result of chest compression or hogtying” (15, p. 50). Stratton et al. (14) were the first to

report sudden, unexpected deaths in the prone hobble (synonymous with “hogtied”) restraint while being transported by medical staff. Three criteria for defining postural or positional asphyxia have been outlined (14,16). First, the person has to be in a position that interferes with pulmonary gas exchange. This could be caused by the obstruction of the airways or by the restriction of the movements of the chest case and diaphragm. Second, the person must have been unable to escape the position. And last, in case of death, other causes, both natural and unnatural, must be excluded with reasonable degree of certainty. This requires a thorough autopsy.

There are some experimental studies of the effects of prone positioning (17–19). Roeggla et al. (17) found a significant impairment of cardiopulmonary parameters (reduced forced expiratory volume, reduced forced vital capacity, end-tidal carbon dioxide increase, heart rate decrease, systolic blood pressure decrease, diastolic blood pressure decrease, and mean cardiac output decrease) after 3 min in the prone hobble restraint position. However, there was no change in oxygen saturation as measured by pulse oximetry. Chan et al. (18) found a restrictive pulmonary function pattern, but no clinically relevant changes in oxygenation or ventilation, concluding that there was no evidence of ventilatory failure, significant hypoventilation, or asphyxiation as a result of body positioning in the restraint position. However, Chan et al. (18) suggested that individuals with large abdominal girths and body mass index > 30 might be at greater risk of development of a restrictive pulmonary function pattern because of abdominal compression from body positioning. A review by the same group concluded that there was no evidence to suggest that body position alone caused hypoventilation, respiratory compromise, or positional asphyxia in the “hogtie” custody restraint position (10). Responding, Howard and Reay emphasized that “... multiple factors, rather than one single cause, play a role in deaths where restraint has been applied” (20, p. 117), and they later brought attention to the importance of the weight force applied by staff during restraint (21). An experimental study with 50 pounds placed on the subject’s back did not lower forced vital capacity or forced expiratory volume in 1 sec significantly or result in hypoxia or hypoventilation (22). Adding 102.3 kg on the back of the subjects significantly lowered mean voluntary ventilation but was described as clinically insignificant (9). Parkes and Carson (19) placed participants face down and applied the body weight of the restraining persons on the upper torso, with and without a flexed restraint position (“Figure four leg lock” which is similar to the prone “hogtied” restraint position), concluding that some, but not all, prone restraint positions significantly restricted lung function.

In 2000, O’Halloran and Frank (15) reported 21 cases of asphyxial deaths during prone restraint. One of the common elements was pressure applied to the upper torso. Following a discussion regarding the scientific basis of the concept of restraint asphyxia (23,24), a case report described the death of a patient manually restrained in the prone position with a heavy weight applied to his back (25). The autopsy disclosed minor external injuries and old inferior frontal cerebral contusion scars, but no cardiovascular or other organ injuries that could explain death. Miyaishi et al. (26) described the death of a prisoner restrained in the prone position. The autopsy disclosed typical findings of thorax compression with intramuscular hemorrhages on the back and multiple fractures of the ribs. No evidence of neck compression/smothering was found, and it was suggested that the cause of death was compression of the thorax. In sum, the restraint asphyxia theory has been debated, most have sug-

gested that the prone position alone is not sufficient to cause significant asphyxia but have believed it to be a contributing factor. The mechanism of compression asphyxia seems to be less controversial.

Our case is somewhat different from most of the previously published cases. As there were several trained mental health workers present, among them one medical doctor, and the patient survived, we were able to recollect and describe the episode fairly detailed. This gives us a unique basis of information in discussing the different hypothetical causes for the near death occurrence. A range of different diagnoses can be considered in this case. The treating clinicians considered the patient's condition to represent an exacerbation of his paranoid schizophrenia. He was very psychotic with anxiety and agitation, but he did not have fever, fluctuating confusion, neuromuscular symptoms (tremor, myoclonic jerks, and muscular rigidity), or typical catatonic behavior. Although they should be considered, on the basis of the information now available, we feel the following differential diagnoses to be unlikely in this case; acute exhaustive mania, excited delirium, Bell's mania, catatonia, sympathomimetic poisoning, neuroleptic malignant syndrome, central anticholinergic syndrome, and serotonin syndrome.

The immediate cause for the patient's cyanosis and loss of consciousness must have been either asphyxiation (i.e., respiratory arrest), cardiac dysfunction (i.e., cardiac arrhythmia or asystole with reduced cardiac output), or a combination of the two.

Clinical information about his heart function during the episode could have clarified the issue. Understandably, ECG-monitoring during the episode would not have been feasible. Examination of peripheral pulse could have contributed with relevant data. However, carotid pulse examination is an inaccurate method of confirming the presence or absence of circulation (27). There was no indication of heart disease or hypertension prior to the episode. The patient was hemodynamically stable shortly after regaining consciousness. From the limited information available, there were no positive findings indicating a cardiac etiology. Still, we have to consider the possibility of arrhythmia. The patient used four different psychotropic drugs, three antipsychotics (clozapine, chlorpromazine, and levomepromazine) and one antidepressant (escitalopram). Sudden unexpected death in psychiatric patients treated with antipsychotics has been a concern for several decades (28). The cause is believed to be ventricular fibrillation (28). A prolonged rate-corrected QT interval on the ECG (QTc) is a surrogate marker for a predisposition to polymorphic ventricular arrhythmia (torsade de pointes) which can progress to ventricular fibrillation (29). Virtually all antipsychotics can cause QTc interval prolongation (28). Our patient did not have QTc interval prolongation, but that does not completely exclude the possibility of a cardiotoxic effect causing arrhythmias as these may in some cases develop without QTc prolongation (30). The use of several antipsychotics simultaneously in the same patient is far from optimal and ought to be avoided. Nevertheless, this treatment strategy is occasionally used to help nonresponding or poorly responding patients, especially when there is a need to sedate the patient (12). Our patient was on three antipsychotics with relatively strong anticholinergic effects. This could have decreased parasympathetic tone, thereby giving preponderance to the patient's sympathetic tone. Autonomic dysregulation as a result of sympathetic hyperactivity and/or parasympathetic hypoactivity has been associated with arrhythmic effects (31). None of the drugs had direct sympathomimetic effects, but the patient's psychological stress might have caused a catecholamine rush thereby adding to the total

sympathetic tone acting on the heart. Even though we lack information about the patient's cardiac function during the episode, drawing on the data that is available, we consider cardiac arrest or arrhythmia to be less likely.

It is a central question to what degree the patient's respiration was compromised. He was brought flat on the floor in the "spread-eagle" position with two staff members (body weight about 80 kg each) lying on his torso, thereby compressing both his chest and abdomen to the ground. The patient remembered having difficulty breathing just before losing consciousness. Two pathophysiological mechanisms had the potential for causing significant respiratory embarrassment. First, restriction of thoracic cage expansion resulting from the fixed body position with a heavy weight on his torso (19). Second, impaired diaphragmatic movement due to increased intra-abdominal pressure. The patient was obese with a protuberant abdomen. Obesity is considered a possible risk factor for asphyxiation during restraint (24), particularly as it may compromise diaphragmatic motion in the prone position because of excessive fat adding to the increased intra-abdominal pressure. The vomit on the patient's face that was noticed after CPR was terminated indicated regurgitation of gastric contents. This is in accordance with an assumption of a significantly increased intra-abdominal pressure.

Another consequence of increased intra-abdominal pressure could be compression of the inferior vena cava causing reduced venous blood return to the heart and subsequently an impaired cardiac output. This mechanism, the inferior vena cava syndrome, has been suggested as a cause of sudden death during restraint with prolonged external compression of the lower torso (32). An experimental study on healthy, athletic young men demonstrated a negative correlation between the amount of weight applied (gradually increased from 5 to 25 kg) to the lower torso and the diameter as well as the maximum blood flow in the inferior vena cava (32). We cannot exclude the possibility of this mechanism, although ill-defined, having been of importance to the patient in our case.

There are additional factors that might have contributed to the patient's inability to maintain adequate respiration; He was exhausted and fatigued after several days, being driven with a high level of physical activity and minimal sleep. Moreover, the total dosage of antipsychotic medication given was high, probably adding to his fatigue.

There was no clear indication of upper respiratory tract obstruction. The patient's head was placed in the proper position, that is, rotated to the side, while a member of staff kept visual and verbal contact with him until he became unconscious and cyanotic. Neither do we have any reason to believe drug abuse to be a contributing factor. The strict management and surveillance at the unit would have revealed such abuse. However, a toxicological analysis would have been conclusive.

From the available data, we assume that the patient developed asphyxia secondary to the physical restraint. The compression of the torso (i.e., the thorax and the abdomen) was probably more important than the prone position itself in causing the asphyxia. Experimental studies (9,18,22) have suggested that restraint in the prone position alone causes a restrictive pulmonary function pattern, but no clinically relevant changes in oxygenation or ventilation.

The American Psychiatric Association Committee on Patient Safety (33) has warned against restraining a patient in the prone position on the assumption that it can cause "suffocation" (p. 10). The National Institute for Clinical Excellence (NICE) in Great Britain (34) also warned against restraint, but chose not

to present one position as safer than another because “the evidence base surrounding the dangers of positional restraint is weak” (p. 98). The NICE Guideline Development Group believed there were dangers related to restraint in any position and therefore discouraged restraint for prolonged periods in any position.

There have been several reports of sudden, unexpected deaths occurring in restraint situations in the last two decades (2,3,5,6,35,36). This case illustrates a situation where physical restraint in the prone position seemed unavoidable, and almost ended fatally. Close monitoring of the patient’s clinical status, rapid release of the restraint when the patient showed signs of asphyxiation, and immediate implementation of CPR prevented a more negative outcome. Actually, the mere release of the restraint might in itself have been sufficient. In retrospect, it is natural to ask if the episode could have been prevented. We cannot exclude the possibility that using different psychotropic medications and/or having a more strict isolation regime with even more staff present in the immediate surroundings of the patient could have been prophylactic with regard to the patient’s aggression.

A further consideration is monitoring once restraint has been implemented. Masters and Wandless (37) and Masters (38) have advocated the use of portable pulse oximeters to monitor oxygenation during restraint, and it is possible that using such equipment in the present case could have been clinically useful. Our hospital has local guidelines for handling aggression and violence. While there are no national Norwegian guidelines, protocols and guidelines appear to be relatively similar throughout the country, and the main principles appear to be in line with current U.K. and U.S. guidelines (33,34). Although there is little Norwegian legal precedent, we believe that if the patient had died, the manner of death would most probably have been listed as an accident. This case report, we hope, can be a relevant contribution to the discussion of the hazards of physical restraint and the possible causes of fatal outcomes.

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Article 4

CASE REPORT

Open Access



Probable clozapine-induced parenchymal lung disease and perimyocarditis: a case report

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Abstract

Background: Clozapine is the archetypical atypical antipsychotic, its primary indication being treatment resistant schizophrenia. Severe side effects caused by clozapine, including leukopenia, agranulocytosis, and myocarditis, are well known. A rarely described side effect is concurrent perimyocarditis and parenchymal lung disease.

Case presentation: A previously physically healthy 23-year-old male Caucasian that suffered from schizophrenia presented with flu-like symptoms 1 week after starting clozapine treatment. Treatment with clozapine was discontinued. He developed respiratory distress. Investigations showed significant parenchymal infiltration in both of the lungs, pericardial fluid, and heart failure. He initially received treatment for suspected malignant neuroleptic syndrome and later for suspected infection, but these tentative diagnoses were not confirmed. The patient's condition gradually improved. In retrospect, clozapine-induced parenchymal lung disease and perimyocarditis were deemed the most probable causes.

Conclusions: Concurrent perimyocarditis and parenchymal lung disease are rare side effects of clozapine. Clozapine-induced disease in general is considered an exclusion diagnosis. Lacking a verifiable diagnosis when suspecting a side effect of clozapine, clinicians might treat the most likely and serious condition presenting and consider discontinuing clozapine until the diagnostic uncertainty is reasonably resolved.

Keywords: Clozapine, Case report, Side effects, Pericarditis, Perimyocarditis, Diffuse parenchymal lung disease, Schizophrenia

Background

Clozapine is the archetypical atypical antipsychotic, its primary indication being treatment resistant schizophrenia. The risk of leukopenia and agranulocytosis in clozapine treatment is well established, affecting approximately 3.0 and 0.5% of patients, respectively [1, 2]. Accordingly, all patients should routinely undertake blood samples. Clozapine induced myocarditis is a recognized, though perhaps overlooked, adverse effect of clozapine. Twenty years ago the prevalence was estimated at less than 0.1%, but increased awareness and research has revealed that the actual prevalence may be as high as 3.0% [3, 4]. The frequency of pericarditis caused by

clozapine is yet to be established and we are aware of less than 10 cases that have been reported [5–7]. However, comorbid pericarditis and myocarditis precipitated by the same aetiological factors (drugs, virus, ischemia, etc.) and with common pathogeneses is not unusual. Given the prevalence of clozapine-induced myocarditis, the prevalence of pericarditis as an adverse effect of clozapine might be higher than the number of published case reports indicates. Clozapine-induced lung disease seems to be exceptional, given the fact that only a handful of cases have been published [8–10]. On the other hand, there might be a lesson to learn from the steady increase in reports of drug-induced lung disease in general. In 1972, only 19 drugs were known to cause lung disease [11]. Five years ago, the number had risen to approximately 350, whereas today more than 600 drugs are recognized as potentially pneumotoxic [12]. In the early 1960s, the first reports of pulmonary

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damage caused by tricyclic antidepressants were published, whereas today most psychotropic drugs are considered potentially pneumotoxic [13]. Case reports serve important functions, including reporting new or rare findings that may be of importance to clinicians and others [14–16]. Treatment with clozapine can result in a myriad of side effects and symptoms, often making clinical assessment difficult. This is even more the case when several organ systems are involved and the suspected conditions are considered highly infrequent. This case report demonstrates the challenges facing clinicians in such a case.

Case presentation

A 23-year-old Caucasian man, diagnosed with schizophrenia and without any prior history of cardiac or pulmonary disease, was transferred from a psychiatric ward to an intensive care unit with flu-like symptoms, i.e., fever (39.7–40.2 °C), nausea, non-productive cough, headache, and muscle pain. The symptoms had developed approximately 1 week after monotherapeutic clozapine-treatment was initiated, and at the time of admittance the daily dose was 300 mg. Initial blood sampling demonstrated elevated levels of creatine kinase (2948 IU/L, range 50–400), C-reactive protein (154 mg/L, normal value <5), lactate dehydrogenase (359 IU/L, range 105–205), aspartate amino transferase (76 IU/L, range 15–45), erythrocyte sedimentation rate (24 mm/h, normal value <13), and myoglobin (248 µg/L, range <100), whereas white blood cells were in the normal range ($9.9 \times 10^9/L$, range 4–11). Blood and urine cultures were negative. Saturation of peripheral oxygen (SpO₂) was 97%. Clinical examination revealed an elevated systolic blood pressure (178/75 mmHg) and tachycardia (120–130/min), but was otherwise normal, as were chest x-ray and electrocardiography (ECG). The patient had no obvious mental symptoms or autonomic instability. Despite the clinical picture being non-characteristic, malignant neuroleptic syndrome was suspected. Hence, clozapine was discontinued and treatment with oral bromocriptine (a dopamine agonist) was commenced with a dose of 2.5 mg three times a day. Clinically, the patient's overall condition worsened in the next 24 h, and he reported dyspnoea and respiratory-dependent chest discomfort. Saturation of peripheral oxygen dropped to 88%. Troponin T was now elevated (0.41 µg/L, normal value <0.03), as were fibrinogen (5.8 g/L, range 2–4), D-dimer (3.7 FEUµg/mL, normal value <0.5), and white blood cells ($11.1 \times 10^9/L$), with a mild eosinophilia ($0.46 \times 10^9/L$, range 0.04–0.4). On the other hand, creatine kinase had fallen (997 IU/L) and myoglobin had normalised (46 µg/L). Extensive testing for various infectious agents, such as streptococcus, coxsackie A and B virus, Epstein-Barr virus, adenovirus, influenza A and B virus, parainfluenza 1 and 3 virus, parvo B19 virus, mycoplasma pneumoniae,

chlamydia pneumoniae and cytomegalovirus, were undertaken without any pathogen identified. Likewise, repeated blood and urines cultures were negative. Given the fact that the patient had been in intramural psychiatric care for 2 months prior to the debut of his somatic symptoms, causes like exposure to toxins, substance abuse and other (prescribed or non-prescribed) drugs were believed to be unlikely. At examination, the patient had tachycardia (129–140/min), fever (39.7 °C) and prolonged exhalation with crepitation and diminished respiratory sounds over the lungs. The chest x-ray revealed significant parenchymal infiltration in both lungs (Fig. 1).

Echocardiography depicted a left ventricular ejection fraction of 54% (a.m. Simpson) and pericardial fluid. Notwithstanding the lack of a demonstrable infective agent and inconclusive blood samples, an infection was presumed. Accordingly, malignant neuroleptic syndrome was considered less likely. Thus, bromocriptine was suspended and intravenous antibiotic treatment with a cephalosporin, cefotaxime, started, with a daily dose of 6000 mg. The next couple of days there was little clinical change, but troponin T (0.20 µg/L) and white blood cells returned to normal, though still with a relative increase in eosinophils: 3.02 and 3.54% at day 3 and 4, respectively, compared to 0.50% the day before admittance and 0.56% at the day of admittance. C-reactive protein remained high (198–201 mg/mL). Echocardiography now exhibited biventricular hypokinesia and dilatation with mitral and tricuspid valve insufficiency, a left ventricular ejection fraction of 34% (a.m. Simpson), and increased pericardial fluid. Chest x-ray displayed regression of the parenchymal infiltration in both lungs. In the following week, there was a gradual improvement in the condition of the patient. The fever dissipated, his breathing became unrestricted and subjectively the patient felt much better. Correspondingly, the blood samples and chest x-rays normalized. Hence, after 8 days of treatment, the intravenous cephalosporin was



Fig. 1 Chest x-ray. Chest x-ray showing massive diffuse parenchymal infiltration, predominantly of the left lung

terminated and the patient transferred back to the psychiatric ward. Repeated follow-ups during the next 4 years demonstrated blood samples within normal range and chest x-rays without identifiable pathology. Echocardiographies, however, showed a persistent cardiomyopathy with left ventricular hypokinesia and a left ventricular ejection fraction (a.m. Simpson) of 42–45%.

Discussion

Adverse effects of clozapine can present with a multitude of symptoms, thus mimicking a wide array of conditions, as partially demonstrated by our case report. Even serious side effects may have an insidious onset, making early detection challenging. This is complicated by the fact that the physical health of patients with severe mental disorders often is poor, and comorbid somatic conditions such as obstructive lung disease and cardiovascular disease are common [17, 18]. At that, these patients are less likely to report somatic symptoms [19]. As a general rule, clozapine should always be suspected as a potential culprit when a patient develops new or worsened physical symptoms, in particular when the symptoms point to a systemic process and appear in the early stages of treatment. Most cases of myocarditis, pericarditis and lung disease seem to develop within 2 to 3 weeks of commencing clozapine [20]. It should also be taken into account that the concomitant use of psychotropic drugs adds to the risk of developing serious adverse effects, as does comorbid metabolic syndrome, heart and lung disease [21–25].

In this case, the diagnostic assessment was challenging. Throughout the process, there was a certain level of diagnostic doubt. Several diagnoses were deliberated, clozapine-induced disease included. The latter, however, has no pathognomonic clinical, biochemical, physical, radiographic or histologic markers. In our case, the clinicians could not rule out an infection and consequently chose the safer option: antibiotic treatment. Apparently, the patient seemed to respond to this treatment, but testing for an infection did not identify an infective agent. In retrospect, we did a thorough clinical review of the case in collaboration with cardiologists and pulmonologists. As a result, parenchymal lung disease and perimyocarditis were deemed the most likely diagnoses. Specifically, the temporality of the drug treatment and the clinical development, combined with the biochemical, radiological, and echocardiographic findings strongly indicated adverse effects of clozapine as causative. This hypothesis was strengthened when the Naranjo Adverse Drug Reaction Probability Scale estimated the causation as probable [26]. One lesson to take home from this case report might be that clozapine-induced disease is an exclusion diagnosis. Accordingly, lacking a verifiable diagnosis, the clinician should treat the most likely and potentially dangerous

condition at any given moment, at the same time discontinue clozapine until diagnostic uncertainty is reasonably resolved.

Several investigations are relevant when suspecting a clozapine-related lung and/or heart condition. Introductorily, it should be noted that reports indicate that inflammation may precipitate clozapine toxicity, possibly due to a cytokine-mediated inhibition of cytochrome P450 1A2 [27]. Consequently, even moderate doses of clozapine could produce significant increase in serum levels in the presence of inflammation.

Elevated levels of C-reactive protein (incl. high-sensitivity C-reactive protein), erythrocyte sedimentation rate and plasma viscosity, are non-specific markers of inflammation. So are white blood cells, but despite the dominant hypothesis of a type I Ig E-mediated acute hypersensitivity reaction, there is no specific level or pattern of white blood cells signalling an adverse effect of clozapine. In other words, eosinophilia, or any other white blood cell pattern, may or may not be present [28]. On the other hand, the presence of eosinophilia in peripheral blood does make the diagnosis of a clozapine-related heart condition more likely, as demonstrated in the majority of documented cases [29]. Markers of myocardial damage such as myocardial muscle creatine kinase, myoglobin and troponins may be useful, but do not represent an unequivocal identification of myocarditis, nor pericarditis. Troponins, for instance, have a high specificity for myocardial damage, but the sensitivity for acute myocarditis and pericarditis is approximately 50 and 30%, respectively [30, 31].

Biopsy of heart and lung tissue may identify ongoing inflammation, but sampling error and interobserver variability in sample interpretation remain significant limitations to its diagnostic value. Furthermore, there is a certain risk of complications [32–35]. Hence, biopsying is not routinely undertaken when clozapine-triggered disease is suspected, but may be necessary in order to home in on the diagnosis. For instance, transbronchial biopsy may aid in the diagnosis of other pulmonary diseases such as pneumonia, sarcoidosis, etc. The same goes for bronchoalveolar lavage. It is especially helpful in differential diagnostics, primarily by excluding infective aetiology to pulmonary infiltrates, secondarily to demonstrate drug-induced eosinophilic pneumonia.

The ECG is widely used as a screening tool for cardiac pathology, despite its low sensitivity.

There are no characteristic ECG patterns in myocarditis and findings range from non-specific T-wave and ST-segment changes, to ST-segment elevation mimicking myocardial infarction, as well as supraventricular and ventricular arrhythmias, QTc prolongation, abnormal QRS configuration, etc. [36]. On the other hand, ECG, as well as echocardiography, could be inconspicuous in the presence of low-grade inflammation of the heart.

Nevertheless, they are simple, low-risk procedures and ECG is generally recommended as a standard procedure before and during clozapine-treatment.

Cardiovascular magnetic resonance (CMR) enables detection of various non-specific features of myocarditis and pericarditis, though the sensitivity is variable, depending on the level of damage [37]. Nevertheless, CMR is preferable to chest x-ray and is the investigation of choice when myocarditis is presumed. Chest x-ray is typically obtained when drug-mediated pulmonary toxicity is suspected, but high-resolution computed tomography (HR-CT) is more sensitive than chest radiography for defining abnormalities [38, 39]. However, the sensitivity is time-dependent and repeated HR-CTs may therefore be necessary. For unknown reasons, HR-CT was not performed in this particular case, which in hindsight should have been undertaken in order to clarify the diagnosis. It is worth remembering that diffuse parenchymal lung changes is just one of many patterns that drug-induced lung reactions may assume [40]. Hence, radiological changes must be considered in conjunction with anamnestic, clinical and investigative information to determine the nature of pulmonary complications.

On pulmonary function tests, toxicity from most drugs result in a restrictive lung disease pattern, with a decrease in total lung capacity. Despite being sensitive to early changes in drug-induced lung function, these tests are unspecific and provide limited diagnostic information. Nonetheless, a pulmonary test could be useful in monitoring treatment.

In summary, when faced with the possibility of clozapine induced heart and/or lung disease, various and repeated investigative procedures are needed to make a qualified clinical assessment.

Conclusions

In treatment-resistant schizophrenia, clozapine is often the drug of choice. However, the clinician should keep in mind the drug's potentially deleterious side effects. Clozapine-induced diseases have no pathognomonic features, initially often masquerading as innocent infections such as the common cold or the flu. Even severe side effects might be difficult to pinpoint as clozapine related. In our case, the evidence of clozapine-induced lung disease does not seem as strong as the evidence of perimyocarditis. Besides discontinuing clozapine, no specific treatment has proven effective against adverse effects of clozapine. Thus, treatment is supportive and symptom-oriented. Myocarditis is an important risk factor for cardiomyopathy. Hence, follow-up is mandatory for all patients who have undergone myocarditis [41].

Abbreviations

CMR: Cardiovascular magnetic resonance; ECG: Electrocardiogram; HR-CT: High resolution computed tomography

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Availability of data and materials

This is a single-patient case report. Data sharing is not applicable to this article as no datasets besides those reported in the article were generated or analysed during the current study.

Authors' contributions

EB, TN and RW all contributed to conception and design, drafting and revising the manuscript, and approving the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Written informed consent was obtained from the patient for the case report.

Ethics approval and consent to participate

Written informed consent was obtained from the patient for the case report. A copy of the written consent is available for review by the editor of this journal. The study was approved by the Data Protection Officer of the University Hospital of North Norway (Approval no. 0600), who also found the report exempt from ethics committee review.

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Article 5

CASE REPORT

Open Access



Clenched fist syndrome: a case report

Trygve Nissen^{1,2} and Rolf Wynn^{1,2*} 

Abstract

Background: The clenched fist syndrome/psycho-flexed hand, first described in the early 1980s, has not yet entered the major psychiatric textbooks. Curiously, the phenomenon has been illuminated mainly in journals and textbooks on hand surgery. There is a need to examine, describe, and understand this syndrome from a psychiatric perspective.

Case presentation: We present a case we encountered in an intensive care unit. A 60-year-old white man with schizophrenia, cerebrovascular disease, diabetes mellitus type 2, and peripheral neuropathy, developed rather acutely bilateral clenched fists in the aftermath of a traumatic dislocated hip fracture that was operated on. He later died due to complications from the surgical procedure.

Conclusions: While this was a complex case with some clinical uncertainty regarding the cause of our patient's symptoms, we conclude that psychological processes were central to the development of his clenched fists. The phenomenon of clenched fists and our case are discussed with reference to the accumulated literature on psychogenic hand disorders and the *International Statistical Classification of Diseases and Related Health Problems*, 10th version. The nosological status appears to be obscure. This case presentation is a first step in increasing the understanding of this syndrome from a psychiatric perspective.

Keywords: Clenched fist syndrome, Psycho-flexed hand, Conversion disorder, Factitious disorder

Background

Medical disorders mimic psychiatric ones, and vice versa. In an often quoted article, the Canadian psychiatrist Erwin K. Koranyi wrote: "No single psychiatric symptom exists that cannot at times be caused or aggravated by various physical illnesses" [1]. The causality can go in the opposite direction as well. Often physical symptoms and signs are caused or aggravated by psychological factors or psychiatric illness. And sometimes the psychiatric symptoms are less prominent than the physical signs. In conversion or dissociative disorders, patients can have various physical signs, for example paralysis or anesthesia, and still be unconcerned about their impairment, that is, feel no or only minor subjective suffering. This phenomenon or sign of calm acceptance has been called "*la belle indifférence*." Its presence can be helpful in the diagnostic work-up although some researchers have disputed its assumed high prevalence in conversion disorders [2].

We encountered a patient with clenched hands that challenged our diagnostic skills. As the literature on the subject is parsimonious, we feel obliged to report our case to the medical community. Clinical case reports can be very useful in detecting rare disorders and generating hypotheses and may give an in-depth understanding of significant educational value. The case report genre appears to be the most appropriate method for conveying our observations [3–5]. The case report follows the CARE guidelines [6].

Case presentation

A 60-year-old white unmarried man with chronic schizophrenia fell to the floor and was unable to get up or walk. When examined he had an asymmetrical smile and apparent paresis of his left leg. He was hospitalized with a tentative diagnosis of stroke.

Past history

From his relatives we learned that he had grown up in a village on the Norwegian coastline as the fourth of five siblings. He did not excel at school, and started at an early age to work in the local fishing industry. He held the job until at the age of 30 he moved to another part

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of the country. There he worked as a custodian at a hotel. At age 37 he went back to his home village to live close to his compassionate family of origin. He was then employed as an assistant custodian (supported employment) in the local fishing industry until he was 56-years old. He was treated for psychotic symptoms on-and-off from his mid-twenties. He was not diagnosed as having schizophrenia until he was 40-years old. Since then he received out-patient psychiatric treatment until the present illness occurred. At the age of 55, diabetes mellitus type 2 was diagnosed. Osteoporosis was diagnosed 2–3 months prior to the present illness.

Present illness

This was the first time he had been hospitalized. His family members said that he had had swallowing problems, difficulties with speech, and unsteady gait for the last 4–5 years. This information was corroborated by our patient's general practitioner. He had deteriorated physically over the last 3–4 months with increased fatigue. He had developed general inertia and was easily exhausted after a short period of physical labor. He had developed hypersomnia, with 10–12 hours of sleep per night, a weight loss of 4–5 kg, and an unsteady gait. To descend the stairs he preferred to sit on his buttocks and slide down the staircase one step at a time until reaching the lower floor. He had been a heavy tobacco smoker for several decades. His alcohol use was modest.

His main psychiatric symptoms before being hospitalized were social withdrawal and delusions about several small persons, the size of dolls, attached to his body. Furthermore, he had auditory and visual hallucinations. He was very reluctant to talk about the contents of the, probably imperative, auditory hallucinations. Antipsychotic medication, risperidone tablets, was first started in 1997. A year later the medication was switched to olanzapine tablets. The dosage varied between 7.5 and 15 mg per day without any objective or subjective side effects. There had been no unambiguous extrapyramidal side effects.

On physical examination, he was alert and orientated, but in some pain in his left hip and knee. He was afebrile with a body temperature (ear) of 37.4 °C, blood pressure was 136/83 mmHg, he had a regular pulse rate at 82 per minute, and oxygen saturation (SaO₂) was 97%. Auscultation of his carotid arteries revealed no bruits. His heart rhythm was regular without any pulse deficit. There were no heart murmurs. A lung examination was sub-optimal as inspiration was weak. It was possible that some crackles could be heard bilaterally at the base of his lungs. A neurological examination revealed impaired tongue wiggling when tested for quick side-to-side movements, dysarthria, symmetrically reduced muscle force (5-/4+) in his upper extremities, reduced force in his left leg (not quantified), and asymmetrical plantar

reflexes (downward movement on the right side, indifferent on the left). His regular medication before admission was olanzapine tablets 12.5 mg/day (7.5 mg + 5 mg), metformin tablets 500 mg three times a day, calcium/cholecalciferol 500 mg/400 IU tablets two times a day, and paracetamol 500 mg two times a day. His complete blood count was normal: hemoglobin (Hgb) was 14.0 g/dL, hematocrit was 0.44, his white blood cell count was $8.2 \times 10^9/L$, his platelet count was $275 \times 10^9/L$, his neutrophil count was $5.6 \times 10^9/L$, his lymphocyte count was $1.5 \times 10^9/L$, his monocyte count was $0.7 \times 10^9/L$, his eosinophil count was $0.4 \times 10^9/L$, and his basophil count was $< 0.1 \times 10^9/L$. The only pathological tests from the chemistry panel were a low creatinine level of 59 μmol/L (reference range, 60–105), a high glucose level of 10.0 mmol/L (reference range, 4.0–6.0), a high glycated hemoglobin (HbA1c) level of 7.5% (reference range 4.3–6.1), a high alanine transaminase level of 94 U/L (reference range 10–70), and a high alkaline phosphatase level of 130 U/L (reference range 35–105). Urine, collected from a urine catheter on the day of admission, was delivered immediately to the microbiology laboratory in the same hospital building, and cultivated. There were >100,000 bacteria per ml, identified as *Staphylococcus epidermidis*, probably representing contamination. There was no bacterial growth in a repeat urine test taken 3 days later.

The day after admission a left dislocated hip fracture was identified. This information, in combination with a normal cerebral magnetic resonance imaging (MRI) and disappearance of his facial asymmetry, caused the clinicians to reject the stroke hypothesis. His hip fracture was operated on the following day. Antibiotic medication (cefalotin 2 grams administered intravenously) was given twice: at the beginning and at the end of the surgery. Blood cultures with two sets, each consisting of one aerobic and one anaerobic bottle (Virtuo® blood culture, bioMérieux), were taken from his antecubital veins the day after admission. The cultures were brought to the microbiology laboratory immediately for further cultivation. No bacterial growth was seen.

Although the hip surgery was technically successful, it was not possible to physically mobilize our patient. The 12th day after hospital admission, a psychiatrist was consulted as our patient suffered from clouding of consciousness, episodic agitation, and increased anxiety. Olanzapine tablets were increased from 12.5 mg to 15 mg per day. On day 15 he was transferred to an acute psychiatric ward as it was considered the appropriate place for further treatment. This was unsuccessful as he deteriorated physically. As a consequence, he was returned to the intensive care unit. He was diagnosed as having bilateral lung emboli and suspected sepsis. New blood cultures were taken. Cefotaxime administered

intravenously, 1 g three times a day, was started on day 18. Two days later, the cefotaxime dosage was increased to 2 g three times a day. The blood cultures revealed no growth.

Unfortunately, from now on a clinical downhill course followed. Our patient got aspiration pneumonia and was unable to swallow food or fluids. It was decided to stop further oral nutrition (fluids, food, pills) in an attempt to prevent further aspirations to his lungs. Instead, total parenteral nutrition was started. The tentative neurological diagnoses being discussed at this point were motor neuron disease, diabetic neuropathy, and extrapyramidal side effects of antipsychotics.

On the 20th day, a neurological examination found only slightly reduced muscle strength (grade 4–4+) for adduction and abduction of his shoulders bilaterally and a tendency to lead pipe rigidity in his wrist joints. No conclusive diagnosis was made. Three days later (day 23), a repeat neurological examination by another neurologist showed essentially the same clinical picture. The lead pipe rigidity in his upper extremities lessened significantly, almost to normal muscle tone, when our patient managed to relax. However, his wrist joints were strongly flexed and his hands tightly clenched to the bed rails bilaterally. Still, no conclusive neurological diagnosis was made. A videofluoroscopic swallow study and an assessment by a speech therapist were suggested but never performed because he did not regain the ability to cooperate.

The 23rd day was also the time for the second psychiatric consultation at the intensive care unit. Our patient was awake with a clear consciousness. He was oriented for time, place, and situation. Rapport was satisfactory. He was relaxed when engaged in a conversation or otherwise taken care of in his room; when left alone, he was stressed and obviously not at ease. He denied hallucinations. However, his dysarthric speech was a hindrance to an adequate psychiatric evaluation. All in all, there had been some improvement in his psychiatric state since the first psychiatric consultation on the 12th day. Haloperidol tablets, sporadically used as on demand medication to calm him, were discontinued. On the 24th day, metronidazole 500 mg administered intravenously was added to the treatment. Both antibiotics were continued through the 28th day, and then terminated.

On the 38th day the neurologist found that the electromyography (EMG) and nerve conduction studies showed changes consistent with a sensorimotor polyneuropathy affecting his lower extremities. There was no EMG pathology in his upper extremities. The EMG/neurography findings were not compatible with motor neuron disease or acute polyneuropathy. No causal explanation for his dysarthria and dysphagia was found.

The one symptom that he confirmed on all psychiatric consultations (that is, on day 12, 23, 31, 32, 35, and 42 after admission) was anxiety. This was a generalized anxiety with fluctuating intensity that responded satisfactorily to diazepam 2–2.5 mg intravenously administered 4–5 times a day. The anxiety stressed him much more when he was left alone in his room. Having a nurse or a family member nearby calmed him significantly. Apart from adding antibiotics for pneumonia, the regular medication was re-evaluated throughout the course. Antidiabetic treatment was switched from metformin tablets to insulin in order to improve his blood glucose level. The antipsychotic medication (olanzapine) was reduced to 10 mg per day as we suspected the drug to be a cause of his hypersomnia and fatigue. Despite a range of efforts from specialists in orthopedic surgery, hand surgery, anesthesiology, pulmonology, neurology, and psychiatry, our patient did not recover. He died 44 days after being admitted to hospital.

The abnormal hand postures

The focus of this case presentation, however, is on the unusual observation of his clenched hands. Thus, we have to step back. During the second psychiatric consultation on day 23 after admission, he was observed clutching his hands onto the side rails of the bed. With some assistance he managed to let go of the rails, but his hands were still tightly clenched. When asked if he could extend his four ulnar fingers he only managed a slight active extension of them, just enough to let the doctor inspect and palpate his palms. On the four later psychiatric consultations, he no longer held onto the side rails. Both hands from now on lay on the duvet with his wrists in palmar flexion, the left one more strongly than the right one. His four ulnar fingers were fully flexed giving the impression of clenched fists (Fig. 1).

During these later examinations, he was still unable to open his hands voluntarily. Neither could he extend his wrists. On testing for passive extension of the wrist joints, proximal and distal interphalangeal joints, and metacarpophalangeal joints of his four ulnar fingers only slight extension was allowed for. His thumbs, however, could be fully extended, although with some resistance.

During the extension of his four ulnar fingers there was a resistance that increased proportionally to the force applied by the examiner, giving it an “elastic feel.” Furthermore, there was a non-pitting swelling on the dorsum of his left hand and lower arm. Passive extension of his fingers allowed for examinations of his palms. There was no visible or palpable sign of Dupuytren’s contracture on either side. Neither were there signs of traumas to the hands. However, he had small wounds in the left fossa cubiti caused by syringes and peripheral venous catheters associated with blood test and intravenous infusions. This

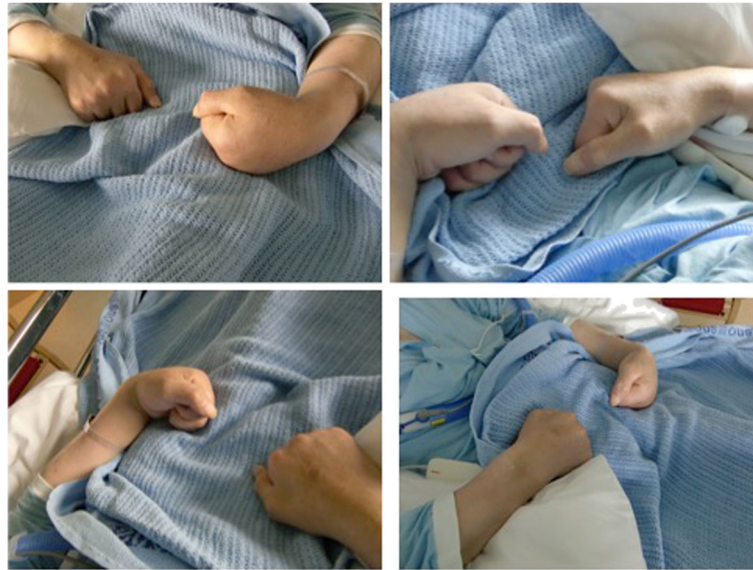


Fig. 1 The patient's clenched fists seen from different angles

could have been the culprit for the abovementioned swelling.

The neurological work-up revealed no plausible organic pathology.

Attempts to treat the clenched hands were obsolete as our patient was unable to cooperate in any way. However, he accepted a palliative application of hand orthoses that counteracted the wrist flexion to some degree during the last week of his life. According to information from family members he had had normal function of his hands prior to this hospital stay. They had a theory that his holding his hands clutched on the side rails was his attempt to prevent falling or being pulled out of his bed. Our patient himself could not explain why his hands were clenched. He had no pain in his hands, but he confirmed having more or less continuous anxiety during all six psychiatric consultations. Every attempt at mobilization in order to get him out of bed failed as he resisted both verbally, by crying out, and physically.

On day 42, a junior doctor at the Department of Hand Surgery responded to a request to examine our patient. After discussing the case with her senior colleagues, the doctor could not conclude on any plausible organic disorder. She recommended putting some insulating material between fingertips and palms to prevent maceration and wounding. She also suggested a repeat neurological examination in case he improved.

An autopsy concluded that the cause of death was aspiration pneumonia. In addition, an old infarction was found in the pons and medulla oblongata. Furthermore, there were discrete thickenings of blood vessels and old, small perivascular infarcts consistent with lacunar state in the brain. His relatives had never observed or heard

our patient report symptoms compatible with stroke or cerebral insults prior to the current illness course.

Discussion

Our patient was hospitalized after a fall that caused a left hip fracture that was operated on. Due to the various medical complications the course of his illness ended fatally after 1.5 months. Three weeks after admission a peculiar phenomenon of strongly clenched fists appeared. As there was no plausible organic cause for this, a psychiatric disorder, clenched fist syndrome (CFS), was suggested. In the literature, the nosological status of CFS is unclear. This case presentation is a first step in increasing the understanding of this syndrome from a psychiatric perspective.

The diagnostic work-up and treatment running parallel during this very sick patient's hospital stay illustrate the complexity of clinical medicine – “medicine-at-work” – when there are several disorders with fluctuating clinical manifestations demanding collaboration by various medical specialists. Clinical medicine very often entails an inherent uncertainty regarding diagnosis, treatment, and prognosis. Although we strive for certainty, we often have to settle for temporary and tentative diagnoses. Thus we feel this report is illustrative of medicine in practice.

Our patient had been a heavy tobacco smoker for several decades and 5 years earlier was diagnosed as having diabetes mellitus type 2. Tobacco smoking and diabetes are risk factors for cerebral (and general) atherosclerosis, and it seems likely that these risk factors could have been the cause of our patient's pathoanatomical findings at autopsy. In hindsight, the brain autopsy findings

might have contributed to his dysarthric speech, dysphagia, and dizziness, maybe justifying a retrospective diagnosis of pseudobulbar palsy. The intermittent slight lead pipe rigidity of his upper left extremity might be explained either by the vascular changes or by his antipsychotic medication.

It is relevant to ask whether the cerebral lesions could have caused the clenched fists. In considering this question we first have to take into account the various relevant differential diagnoses. In order to diagnose an abnormally clenched fist as a non-organic disorder, we ought to exclude these organic disorders: (1) Dupuytren's contracture, (2) collagen diseases, (3) rheumatic arthritis, (4) camptodactyly, (5) arthrogryposis multiplex congenita, (6) progressive systemic sclerosis, (7) eosinophilic fasciitis, (8) cerebrovascular disorders, (9) peripheral nerve injuries, (10) complex regional pain syndrome, (11) corticobasal ganglionic degeneration, and (12) late complication of Parkinson's disease [7, 8].

The slight increase in muscle tone, described in our case as being lead pipe rigidity, was – as already mentioned – possibly caused by the antipsychotic medication. However, the clenching of his fists is not a typical extrapyramidal side effect. Our patient had no known physical disease of his hands prior to the clenching of his fists. The onset was abrupt and symmetrical. The clenching onto the bed rails was most probably motivated by his anxiety. There were no known acute cerebrovascular occurrences prior to the hands clenching. In addition, spasticity following a stroke affecting the upper motor neuron usually takes some days or weeks to develop. Initially, upper motor neuron lesions cause flaccid paresis or paralysis. The muscular contraction of our patient's hands was strong and increased proportionally with the force applied when attempting to extend fingers and wrist joints, that is, qualitatively different from the lead pipe rigidity that was present prior to the clenching. It is hard to conceive of any of the abovementioned diseases (numbers 1–12), other than the cerebrovascular category (number 8), to start acutely and symmetrically. Besides, the abovementioned diseases (that is, numbers 1–7 and numbers 9–12), each have their distinctive clinical features that were not present. In sum, we find it reasonable to consider a psychopathological mechanism the most likely cause. However, the diagnostic work-up of the clenched fists could have been more systematic from the start and throughout the course. Obviously, the “hand problem” was of minor importance compared with all the other serious medical complications.

The conversion disorder we suggest as compatible with our case is variously labelled “CFS” [9] and “the psycho-flexed hand” [10]. This syndrome seems not to have been described in medical or psychiatric literature before E. Mitchell Hendrix and collaborators in 1978

published a case report on the treatment of “an ‘hysterically’ clenched fist” [11]. In 1980 Simmons and Vasile published a case series of five patients [9]. They labelled the phenomenon “CFS” whereas Frykman, Wood, and Miller, based on their case series 3 years later, chose a different term, “the psycho-flexed hand” [10]. The features were very similar, and it appeared obvious that it was essentially the same entity. Today, CFS seems to be the favored term.

There is a variety of psychopathologies affecting the upper extremity. These can be difficult to detect and diagnose correctly. In order to alleviate some of the confusion that can arise, researchers have proposed classifications for these disorders [7, 12, 13]. In 1991, Grunert *et al.* suggested three categories of factitious disorders: (i) factitious lymphedema, (ii) self-mutilation and wound manipulation, and (iii) finger and hand deformities [12]. They put CFS in the third factitious category, that is, finger and hand deformities, although the original publication on the syndrome [9] emphasized it being a *conversion* disorder. The two categories – factitious and conversion – are mutually exclusive. A conversion disorder cannot be a subgroup of the factitious disorders. In 2008, Mary Eldridge and collaborators, among them Grunert, published a “*Streamlined classification of psychopathological hand disorders*” [13] as an up-to-date revision of their classification from 1991. The third category, finger and hand deformities, was wisely relabeled as psychopathological dystonias, which comprised conversion disorders, factitious disorders, and malingering. In other words, the authors acknowledged conversion as a designation for at least some hand disorders.

To clarify, conversion disorders are relabeled *dissociative disorders* according to Chapter V “ICD-10 classification of mental and behavioural disorders” of the *International Statistical Classification of Diseases and Related Health Problems*, 10th version (ICD-10) [14]. If the CFS were to be given status as a formal diagnosis in the ICD-10 classification, the closest fit would be *F44.4 Dissociative motor disorder*. As Eldridge and co-authors note, this disorder is unconsciously motivated and unconsciously produced, while factitious disorders are unconsciously motivated, but consciously produced [13] (see Table 1).

Table 1 Differences between conversion disorders, factitious disorders, and malingering

Disorder	ICD-10 alphanumeric code	Intention/motivation	Production of symptom
Conversion	F44	Unconscious	Unconscious
Factitious	F68.1	Unconscious	Conscious
Malingering	Z76.5	Conscious	Conscious

ICD-10 *The International Statistical Classification of Diseases and Related Health Problems*, 10th version

This makes good sense in theory. Alas, in clinical practice, the distinction is not always that clear. A factitious disorder cannot be diagnosed with certainty unless the patient admits to having produced the physical sign(s), or, alternatively, health personnel have observed this production. Also, it can be hard to find a clear distinction between unconscious and conscious production of symptoms or signs.

Apart from the muscular contraction of flexor muscles in CFS, other major features are [9, 10]:

- A minor physical trauma has often occurred a short time before the fists become clenched.
- A swelling of the hand may occur.
- There may be some maceration of the palm as a result of faulty hygiene.
- There is often pain with passive extension.
- There is usually no pain with passive flexion.
- There are normal findings on EMG and nerve conduction studies.
- EMG may indicate muscle contraction of finger flexors with passive extension.
- Examination performed during anesthesia often reveals a full range of motion.
- Often, only the three ulnar fingers are affected.
- The patient is often relatively unconcerned about his or her dysfunctional hands (*la belle indifférence*).
- All relevant somatic differential diagnoses have been excluded.

The diagnosis of CFS is – at the time being – typological, that is, based on its similarity to those cases that have been described in the medical literature so far. Although not very experienced with conversion disorders affecting the hand, we concluded that our patient most likely had CFS. He had the characteristic clenched hands compatible with the description of CFS. He had had a physical trauma (although not directly to his hands) a few weeks earlier when he fell on the floor. EMG and nerve conduction studies in his upper extremities were normal. All fingers were affected although his thumbs to a lesser degree. The swelling on his left hand was probably caused by repeated blood tests and intravenous infusions administered to several places on his arm. There was no indication that it was self-inflicted.

Descriptive psychiatric diagnoses that have been found to pre-date the onset of CFS are depression, schizophrenia, “obsessive-compulsive character,” and “major depression ... with concurrent dependent and borderline personality disorder” [9, 10, 15]. Psychiatric/psychological evaluation beyond descriptive diagnoses can give some clues to understanding the psychodynamics. In teenagers there is usually a family conflict [3, 9]. Simmons and Vasile noted in their patients “... a consistent

theme of repressed anger ... The hand bound into a fist symbolically expresses anger ...” [9]. The authors also pointed to one of their young patients, a 14-year-old girl having “... rigid mechanisms of avoidance and denial as defences against expressions of impulses” and “... flat rejection that emotional factors could be contributing to her disability” [9]. Patients have also been described as “... introverts, shy, timid, retiring, and unable to express anger” [10]. Grunert *et al.* described a group of 18 patients with psychopathological hand disorders of whom 11 had CFS [12]. Many of these were described as “rather passive, emotionally needy individuals who tended to focus psychological conflicts on physical symptoms.” Another group was characterized as “...angry, hostile persons who were suspicious and tended to act out their anger maladaptively.” The first group had the best prognosis with regard to returning to work after treatment.

As to the predisposing or precipitating psychological factors for our patient’s disorder, we must rely more on our own speculation than on a sound comprehensive anamnesis. Our patient had for several months been apprehensive about walking up and down staircases. This was understandable as he was dizzy and walked unsteadily. After the fall on the floor a series of events occurred that might have caused his anxiety to increase: the hospitalization, the medical work-up including the noisy and claustrophobic MRI, the hip surgery, the postoperative complications including a short delirious episode, and well-meaning health personnel trying to mobilize him against his will. From the perspective of an anxious and psychotic person with delusions, hallucinations, and speech problems, it is not hard to imagine that the hospitalization with all its alienating elements could have been a very stressful experience. This might have activated an acute stress reaction, and an equivalent to the flight, fight, or freeze-response. He could not flee. But he could “fight” to some degree, for instance by yelling out if he saw that he was about to be left alone in his room. Furthermore, maybe his hands clutching onto the side rails was part of a freeze-response. From his perspective, this is a sensible thing to do if you fear that somebody would try to pull you out of your bed, which was his relatives’ hypothesis. As he deteriorated and let go of the side rails, his hands were still clenched. The once adaptive response was no longer adaptive. Why his hands would not open, we cannot easily explain. Or, if he felt that he had had “success” with his clenched fists up until then, why give it up?

If this rather short and simple psychodynamic hypothesis has some validity, we might not have to invoke a more complex psychoanalytic explanation assuming a subconscious intrapsychic conflict resulting in the physical symptom, that is, clenched fists, as a symbolic

representation of this conflict [16]. According to the “law of parsimony,” also called Occam’s razor, the most simplistic theory, that is, the one with the fewest assumptions, will often be satisfactory in practical medicine although spurious from a strictly scientific point of view [17]. Anyhow, to get a better understanding of the psychological underpinnings, we would have had to wait until he was able to communicate better. Unfortunately, he died before we reached that point.

In 2008 Batra *et al.* described the “psychoflexed hand” as “...a rarely described and poorly understood condition, which has been omitted from the latest editions of several hand surgery texts” [18]. However, the authoritative *Green’s Operative Hand Surgery*, authored by S.W. Wolfe and associates, does in fact include this disorder in its chapter on factitious disorders, published in 2011 [19]. Interestingly, neither of the two major textbooks in psychiatry mentions CFS in their most up-to-date editions [20, 21].

Conclusions

Ours was a complex case, and there was clinical uncertainty. However, we believe that the clenching of our patient’s fists is best explained as a conversion disorder, CFS. There is still insufficient clinical data on CFS. Further research should strive to gain more knowledge on etiology, pathogenesis, clinical manifestations, and treatment. Also, the nosological status should be clarified. Should it be labelled a syndrome, a disorder, a reaction, a conversion reaction, a phenomenon, or an entity? All these designations have been used in articles about the CFS/psycho-flexed hand. In itself, that is an indication of the unresolved nosological status. The medical community will hopefully design studies that can broaden our understanding. We also urge the psychiatric community to disseminate the current knowledge, report on further observations, and collaborate with colleagues from other medical specialties that encounter this or similar disorders.

Abbreviations

CFS: Clenched fist syndrome; EMG: Electromyography; ICD-10: *The International Statistical Classification of Diseases and Related Health Problems*, 10th version; MRI: Magnetic resonance imaging

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All data generated or analyzed during this study are included in this published article.

Authors’ contributions

TN supported the management of the patient. Both authors contributed to the production and finalizing of the manuscript. Both authors read and approved the final version.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient’s next of kin for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

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