Epidemiology and health related quality of life in hypoparathyroidism in Norway

Marianne C Astor[1,2], Kristian Løvås[1,2], Aleksandra Debowska[3], Erik F Eriksen[4] Johan A Evang[5], Christian Fossum[6], Kristian J Fougner[7], Synnøve E Holte[8], Kari Lima[9,11], Ragnar B Moe[10], Anne Grethe Myhre[11], E. Helen Kemp[12], Bjørn G Nedrebø[13], Johan Svartberg [14, 15], Eystein S Husebye[1,2]

[1]Department of Clinical Science, University of Bergen, Bergen, Norway, [2]Department of Medicine, Haukeland University Hospital, Bergen, Norway, [3]Department of Medicine, Vestfold Hospital , Norway. [4]Dept of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital, Norway, [5]Section of Specialized Endocrinology, Oslo University Hospital, Rikshospitalet, Norway, [6]Department of medicine, Innlandet Hospital, Gjøvik, Norway, [7]Department of Endocrinology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway, [8]Department of Medicine, Sørlandet Hospital, Arendal, Norway,[9]Department of medicine, Akershus University Hospital, University of Oslo, Oslo, Norway, [10]Department of medicine, Østfold Hospital, Fredrikstad, Norway [11]Department of Pediatrics, Rikshospitalet, Oslo University Hospital, Oslo, Norway, [12]Department of Oncology and - Metabolism, University of Sheffield, Sheffield, UK, [13]Department of Medicine, Haugesund Hospital, Haugesund, Norway, [14]Division of Internal Medicine, University Hospital of North Norway, Tromsø, Norway, [15]Institute of Clinical Medicine, UiT The Arctic University of Norway, Tromsø, Norway.

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Corresponding author:

Marianne Catharina Astor, MD.

Department of Clinical Science.

University of Bergen at Haukeland University Hospital, Norway.

Phone: +47 559 73077

Fax + 47 559 75890.

E-mail: marianne.astor@helse-bergen.no

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Abstract

Objective The epidemiology of hypoparathyroidism (HP) is largely unknown. We aimed to determine prevalence, etiologies, health related quality of life (HRQoL) and treatment pattern of HP.

Methods Patients with HP and 22q11 deletion syndrome (DiGeorge syndrome) were identified in electronic hospital registries. All identified patients were invited to participate in a survey. Among patients who responded, HRQoL was determined by Short Form 36 (SF-36) and Hospital Anxiety and Depression scale (HADS). Autoantibodies were measured and candidate genes (CaSR, AIRE, GATA3 and 22q11-deletion) were sequenced for classification of etiology.

Results We identified 522 patients (511 alive) and estimated overall prevalence at 102 per million divided among post-surgical HP (64 per million), non-surgical HP (30 per million) and pseudo-HP (8 per million). Non-surgical HP comprised autosomal dominant hypocalcemia (21%), autoimmune polyendocrine syndrome type 1 (17%), DiGeorge/22q11 deletion syndrome (15%), idiopathic HP (44%), and others, 4%. Among the 283 respondents (median age 53 years (range 9-89), 75% females), seven formerly classified as idiopathic were reclassified after genetic and immunological analyses, whereas 26 (37% of non-surgical HP) remained idiopathic. Most were treated with vitamin D (94%) and calcium (70%), and 10 received PTH. HP patients scored significantly worse than the normative population on SF-36 and HADS; patients with post-surgical scored worse than those with non-surgical HP and pseudo-HP, especially on physical health.

Conclusions We found higher prevalence of non-surgical HP in Norway than reported elsewhere. Genetic testing and autoimmunity screening of idiopathic HP identified a specific cause in 21%. Further research is necessary to unravel the causes of idiopathic HP and to improve the reduced HRQoL reported by HP patients.

Introduction

Primary hypoparathyroidism (HP) is caused by a group of heterogeneous diseases in which hypocalcemia and hyperphosphatemia occur as a result of insufficient parathyroid hormone (PTH) secretion or receptor dysfunction in target organs. The most common etiologies among adults are surgical damage to the parathyroid glands. Non-surgical HP can be either autoimmune or genetic (Table 1), but in many cases the cause remains unknown, referred to as idiopathic HP.

Epidemiological studies on HP are sparse and mostly cover certain subgroups. In Denmark, the prevalence of post-surgical HP was 220 per million inhabitants, non-surgical HP 23 per million, and pseudohypoparathyroidism (PTH resistance; pseudo-HP) 11 per million (1-3) totaling 254 per million. An estimate among insured people from the US revealed that about 77 000 have chronic HP of all causes (4), which translates into an approximate prevalence of 250 per million. In Japan and Israel, the prevalence numbers of idiopathic HP were 7 and 9 per million, respectively, and of pseudo-HP in Japan 3 per million (5, 6).

Patients with pseudo-HP and vitamin D resistance have elevated PTH, in contrast to classical HP. The clinical picture in pseudo-HP and vitamin D resistance is equal to other forms of HP and is therefore included as a subgroup of HP. Autosomal dominant hypocalcemia (ADH) (7) is probably the most common genetic cause of HP, usually caused by an activating mutation in the calcium sensing receptor (*CASR*), termed ADH type 1, or rarely in guanine nucleotide binding protein, alpha 11 (*GNA11*), termed ADH type 2 (8). Occasionally, *CASR* mutations induce polyuria and hypokalemic alkalosis, called ADH with mild Bartter syndrome type 5. The severity of ADH is highly variable, and asymptomatic patients and those who exhibit mild symptoms can often go undiagnosed.

Autoimmune HP is mainly seen as part of autoimmune polyendocrine syndrome type 1 (APS-1), in which it is present in about 80% (9, 10). About half of the APS-1 patients with HP have autoantibodies against NACHT leucine-rich-repeat protein 5 (NALP5), an intracellular protein with unknown function highly expressed in parathyroid tissue (11). Autoantibodies against interferon omega (IFN-ω)

can be detected in nearly all APS-1 patients regardless of organ involvement (12). Autoantibodies that activate CaSR have also been described as an autoimmune cause of HP (13).

HP may occur as part of various syndromes, most commonly the 22q11 deletion syndrome (DiGeorge syndrome). The prevalence of hypocalcemia among patients with this syndrome varies from 17% to 60% in different reports (14), and most have PTH levels below or in the low reference range (15) due to underdeveloped parathyroid glands. Only a minority requires treatment for chronic hypocalcemia, and only 7% of those with DiGeorge syndrome were diagnosed based on hypocalcemia and HP in a Norwegian national survey (16).

The conventional treatment of HP is calcium and active vitamin D supplementation to alleviate symptoms of hypocalcemia. To ensure normal level of 25-hydroxyvitamin D (25(OH)D) many patients also need supplementation with calciferol, as treatment with calcitriol or alphacalcidiol does not affect the 25(OH)D status. Calciferol is probably important for several cellular processes, as intracellular hydroxylation to active vitamin D occurs in many different cells (e.g. bone, gut, prostate). The well-known neuromuscular problems accompanying vitamin D insufficiency, together with proposed association of vitamin D insufficiency to a number of different conditions like cancer and diabetes mellitus is a reasonable argument to ensure adequate vitamin D status also in HP patients (17). Higher doses of calciferol can also be used instead of active vitamin D, and was the treatment of choice before active vitamin D became available. Calciferol increases the risk of prolonged hypercalcemia, and is now recommended for treatment of HP only if active vitamin D is unavailable.

To minimize the hypercalcuria and hyperphosphatemia following treatment with potent vitamin D analogues, serum calcium should be kept in the low normal range or slightly below. Undertreatment can lead to complications like convulsions and arrhythmias, and overtreatment to tissue calcification with risk of kidney failure (18). PTH replacement therapy is not approved in Europe, but is advocated as a treatment option for patients who are difficult to manage on conventional therapy (17, 19) and since January 2015 recombinant human PTH (1-84) has been approved in the US for treatment of HP.

Given the scarcity of epidemiological data and the unique possibility to obtain nation-wide data in Norway, we aimed to establish the epidemiology, etiology, quality of life and to map current treatment modalities in a nation-wide survey of HP.

Material and Methods

Patients and design

We aimed to identify all living patients with HP in Norway, who had been registered in an electronic hospital registry, as we assumed that the vast majority of the patients would have been admitted to specialist care at least at the time of diagnosis. The health care system in Norway consists of four Regional health authorities that own the health trusts, altogether 19 somatic health trusts, responsible for the hospitals in each region (varying from 1 to 6 hospitals in each trust). Invitations to participate in the study were sent to all but two health trusts comprising five hospitals that were considered too small and also lacked endocrinology departments. The research department in two of the health trusts declined participation (seven hospitals), and one health trust (four hospitals) and three single hospitals did not respond to our request. Thus, we searched the in-patient and out-patient registries at departments of medicine, surgery and pediatrics in 35 of 54 hospitals, including all the tertiary and the majority of the secondary endocrine centers. Altogether 80% of the Norwegian population was covered. In addition, the survey was advertised through the Norwegian HP patient association.

The inclusion period was from October 2010 till September 2013. The search criteria were the International Classification of Diseases version 10 (ICD10) codes E20.0-9 (HP), E21.4 (Other specified disorders of parathyroid gland), E89.2 (post-surgical HP), and D82.1 (DiGeorge syndrome). In two of the university hospitals the search also included codes E83.5 (disorders of calcium metabolism), R29.0 (tetany), P71.0-9 (transitory neonatal disorders of calcium and magnesium metabolism) in addition to ICD 9 codes 252.1, -8, -9 (disorders of the parathyroid gland), 275.40, -41 and -49 (disorders of calcium metabolism), 781.7 (tetany), 775.4 (hypocalcemia and hypomagnesemia in the newborn), 279.11 (DiGeorge syndrome).

Medical records were reviewed and the diagnosis of HP was verified by an endocrinologist in each case. The diagnostic criteria were one of the following: 1) serum calcium below reference range with simultaneously low or inappropriately normal PTH, 2) serum calcium below reference range with simultaneously high PTH and normal renal function (pseudo-HP), 3) criterion one plus need of permanent treatment for more than one year when HP was due to surgery or DiGeorge syndrome. Patients who fulfilled the inclusion criteria were invited to participate in the study and to complete a questionnaire including time of diagnosis and symptoms, treatment, and cause of the disease (if known), the Short Form 36 (SF-36) and Hospital Anxiety and Depression scale (HADS). Blood and urine samples were collected. Non-respondents received a second invitation, and a phone call to ask for willingness to participate. All the participants or their guardians gave written informed consent. The regional committee for medical and health research ethics of Western Norway approved the study, as well as separate approval at each participating hospital trust's research department.

Blood and urine analyses

Serum was analyzed for total calcium, albumin, phosphate, magnesium, creatinine, thyroid-stimulating hormone (TSH) and free thyroxine (FT4). Absolute estimated GFR (eGFR) was calculated based on measured creatinine and calculated body surface according to the formula: Calculated eGFR (Modification of Diet in Renal disease (MDRD) formula) x (0.20247 x height (m) $^{0.725}$ x weight (kg) $^{0.425}$)/1.73, where the MDRD formula is 175 x (s-Creatinine/88.4)$^{-1.154}$ x (age)$^{-0.203}$ x 0.742 (if female). Albumin corrected calcium was calculated from the formula: serum calcium (mmol/L) + 0.02 x (40 – measured serum-albumin (g/L)). In spot urine creatinine and calcium per mmol creatinine was assayed. Assays of autoantibodies against NALP5 and interferon omega (IFN-ω) were performed using radioligand binding assay (20). Calcium-sensing receptor (CaSR) antibodies were tested using immunoprecipitation (21). All the non-surgical patients and a random sample of twenty post-surgical patients were tested for CaSR-antibodies. All patients with available blood samples (n=251) were analyzed for antibodies against NALP5 and IFN-ω.

Sequencing of genes was carried out by Sanger sequencing. The MLPA (Multiplex Ligation-dependent Probe Amplification) technique was used for analysis of large deletions/duplications. DNA

was purified from blood using QIASymphony SP Midi Kit. Sequencing of *CASR* gene and 22q11 were performed in all the patient with idiopathic HP. *GATA3* was sequenced to identify one patient with the syndrome of hypoparathyroidism, sensorineural deafness and renal disease (HDR), and *AIRE* was sequenced in one patient with NALP5 autoantibodies.

Questionnaires

SF-36 is a 36 item quality of life questionnaire with response alternative scores 1-6 for each item. A scoring algorithm transforms the raw score to a score from 0-100 were a high score indicates better HRQoL. Eight scales are calculated: perception of physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH). Missing data were replaced by the mean scores of the completed items in the same scale if at least half of the items in the actual scale were answered. HADS is a 14 items questionnaire, seven for anxiety and seven for depression. Scores are 0-3 for each item, and lower scores are favorable. If a single item from a subscale was missing, the data was replaced by using the mean of the remaining six items. If several items were missing the subscale was discarded. Norwegian normative data are available for both SF-36 (22) and HADS (from the Health Study of Nord-Trøndelag 1995-97, HUNT II) (23).

Statistics

Norway's population in 2012 (4 985 870 inhabitants) was used to calculate the prevalence (Statistics Norway) (24). Two sample t-test and the Mann-Whitney U test were used for continuous data that were normally and not normally distributed, respectively. One way ANOVA was used to determine differences between the means of three or more independent groups, with post hoc analyses by Fisher's least significance difference test or Games-Howell when appropriate. Data are presented as median, unless specified. A significance level at 0.05 was chosen for all tests. Pearson's ρ was calculated for bivariate correlations.

Results

Patient identification and epidemiology

The initial search in two hospital registries using extended search criteria yielded over 2000 hits, but only 132 were verified as HP. For subsequent searches, all ICD9 codes and three ICD10 codes (E83.5, R29 and P71.0-9), were omitted. According to the results from these two centers the narrower search criteria we might miss approximately 8% of the HP patients. Even the narrowed search criteria revealed a coding practice that could not alone be trusted to identify patients. The erroneous coding was mostly attributed to hypocalcaemia of other causes, such as critical illness, malignancy, renal failure and transient HP after surgery.

Altogether 522 patients were identified, of whom 511 were alive at the end of the registration period yielding an overall prevalence of 102 per million of whom 94 and 8 per million were genuine and pseudo-HP, respectively. Post-surgical HP comprised 321 individuals (64 per million) and non-surgical HP 151 individuals (30 per million, pseudo-HP excluded). There were large regional variations in post-surgical HP prevalence (Table 2), which accounts for most of the variation in overall HP prevalence. Among the non-surgical HP patients the largest subgroup was idiopathic (n=67, 44%), while 85 had genetic or autoimmune HP, of which ADH (n=31, 21%), APS-1 (n=25, 17%), and DiGeorge syndrome (n=23, 15%) were most common. Four had HDR, one vitamin D-dependent rickets type 1 and one Stormorken's syndrome (Table 3). The patient with vitamin D-dependent rickets is not included in the further analysis, but is included in tables for completeness. Eight percent of the identified patients with DiGeorge syndrome had permanent treatment for HP of more than one year duration. Ninety percent of the patients were identified through search of hospital registries, whereas 10% were identified from other sources, in particular the patient organization.

National survey

Two hundred and eighty three (55%) agreed to participate (median age 53 years (range 9-89); 75% females). The sex and age distribution of the identified patients and respondents were similar, but post-surgical HP was slightly more common among the respondents (Table 3). Patients with post-

surgical HP, ADH and APS-1 had a response rate at about 60%, whereas the response rates for patients with idiopathic HP, pseudo-HP and DiGeorge syndrome were 35-40%.

Etiology of non-surgical HP

Positive IFN-ω autoantibodies were found in 16 patients, of whom 15 had APS-1 (100%). One had post-surgical HP and had previously been treated for malignant thymoma and myasthenia gravis. NALP5 autoantibodies were detected in 11 patients, of whom seven had known APS-1 (median titer 822, range 787-1555, cut-off 65). One patient with high titer (1020) was diagnosed with idiopathic HP at age 22; all other tested antibodies were initially negative, including IFN-ω. However, sequencing of *AIRE* confirmed two known disease-causing mutations (c.879+G>A and c.967_979del) consistent with APS-1 (10), and a new serum sample taken 2 years after the first was now clearly positive for IFN-ω. Three patients with positive NALP5 autoantibodies and no evidence of APS-1 had low titers (indices 66-161). One patient had positive CaSR autoantibodies, although only a slightly elevated index (2.69, cut-off value 2.26). This patient was later diagnosed with DiGeorge syndrome. Seven patients (21%) formerly classified as idiopathic HP were reclassified after genetic testing. Four had activating mutations in *CASR* (ADH), one had DiGeorge syndrome, one had the HDR syndrome and one APS-1 (see above).

Treatment and follow-up

Calcium supplementation was used by 198 (70%) and active vitamin D formulations by 237 (84%) (Table 4). About half (n=136, 48%) used either ergocalciferol (39%) or cholecalciferol (61%) of whom 102 (75%) in combination with active formulations of vitamin D. Eleven used ergocalciferol in high doses as the only vitamin D source. Ten patients were treated with subcutaneous PTH, of whom three with 1-34 injections, five with 1-84 injections and two 1-84 continuous infusions by pump. There was no significant difference in types of medication used by post-surgical, non-surgical or pseudo-HP patients, except treatment with PTH; nine of them were post-surgical and one non-surgical. Median albumin corrected serum calcium was below the reference range (2.08 mmol/L, reference

range 2.20-2.55), whereas the median urine calcium value was slightly above the reference range (0.51 mmol/mmol creatinine, reference range 0.04-0.50) (Table 4). Post-surgical HP had significantly higher albumin corrected serum calcium and serum magnesium than non-surgical HP patients (P=0.002 and P=0.007, respectively), whereas serum phosphate were similar. Eighteen percent had kidney failure (eGFR <60 ml/min), of whom 98% had eGFR over 30. The median eGFR was 80.8 (14.6-215.7) ml/min. Patients with both post-surgical and non-surgical HP had significantly higher calcium excretion (P<0.001 and P=0.003 respectively) and post-surgical patients also had lower eGFR (P=0.04) than pseudo-HP patients.

The non-surgical patients were younger than the post-surgical HP patients both at the time of diagnosis (median 22 vs 40 years) and at the time of the study (median 48 vs 56 years). Pseudo-HP patients were youngest both at time of diagnosis (median 12 years) and at the time of study (median 32 years). Overall, the median age at diagnosis was 36 years (range 0-81). Most (70%) were diagnosed with HP within the first six months from presentation of hypocalcemic symptoms, but 17% were diagnosed between two and five years after the first symptoms. In 9%, the diagnosis was delayed more than five years. Many patients with non-surgical HP were diagnosed late; 14% between two and five years and 14% more than five years after symptom debut, as opposed to post-surgical HP (corresponding numbers were 5 and 6%, respectively). Among patients with pseudo-HP, 19% and 31% were diagnosed between two and five years and more than five years after symptom debut, respectively.

Most of the patients (64%) were diagnosed by an internist, endocrinologist or pediatrician, but 15% were diagnosed by a general practitioner and 21% by others. A higher percentage of the post-surgical patients were diagnosed by others (24%), primarily a surgeon, but also 16% of non-surgical patients and 7% of pseudo-HP patients were diagnosed by non-internists, mostly neurologists.

The majority (82%) had their serum calcium levels assessed every six months or more frequently. A higher percentage of patients in the surgical group (69%) than the non-surgical (44%) and the pseudo-HP group (53%) reported that urine calcium never had been measured.

Quality of life and working ability

The SF-36 and HADS scores are given in Table 5 as mean ± SD compared with respective Norwegian normative data (22, 23). HP patients had significantly lower SF-36 score than the normative population in all eight dimensions, but pseudo-HP patients in only three of eight dimensions (RP, VT, SF). Overall female patients scored worse than male patients for PF (P=0.03) and VT (P=0.03), whereas patients with post-surgical HP scored worse than non-surgical for RP (P=0.002), BP (P=0.03) and VT (P=0.04) and worse than pseudo-HP for PF and GH (both P=0.03).

HP patients displayed significantly higher symptom score for anxiety, depression and total HADS score than normative Norwegian population. The post-surgical group scored worse on depression than non-surgical (P=0.02). Thirty-eight percent had anxiety scores ≥ 8, and 26% had depression score ≥ 8, indicative of clinical significant anxiety and depression. Nine of sixteen patients (56%) with pseudo-HP had anxiety scores ≥ 8. Gender did not affect the HAD scores significantly.

No correlation between SF-36 or HADS scores (overall and subgroups) were found, neither with corrected calcium levels nor serum magnesium levels. However, there was a weak negative correlation between PF and serum magnesium (Pearson's ρ -0.2; P=0.02) in post-surgical HP patients.

Working ability

Forty percent received permanent or temporary social security benefits (SSB) (Table 4). Among the general population in Norway aged 18 to 66 years the proportion of permanent SSB is about 10% and temporary SSB about 4% (24).

Discussion

We found an overall prevalence of HP in Norway less than half the prevalence recently established in Denmark (1-3) and USA (4). This difference mainly reflects fewer with post-surgical HP in our study, as the prevalence of non-surgical HP was higher than in Denmark (2). Non-surgical HP was most

common in Western Norway, where ADH in a few large families (25) and APS-1 accounted for the difference. These differences could be genuine or due to underdiagnosing in other regions. Higher prevalence of idiopathic and pseudo-HP were found in the Norwegian cohort than in studies in Japan (5), but similar to that found in Denmark (3) and in Israel (6).

IFN-ω autoantibodies were detected in all the APS-1 patients, but also in one post-surgical patient, who had thymoma-associated myasthenia gravis, in which IFN-ω autoantibodies are common (26). In concordance with earlier studies (11), NALP5 autoantibodies were detected in 50% of the patients with previously known APS-1. One patient with a high titer of NALP5 autoantibodies, diagnosed as idiopathic HP 39 years previously tested negative for IFN-ω autoantibodies, but sequencing of *AIRE* confirmed APS-1, and a repeat sample two years later was clearly positive also for IFN-ω autoantibodies.

Despite testing for underlying causes, about one third of non-surgical patients remain idiopathic, which may conceal hitherto unidentified forms of HP. The medical history and clinical vigilance can to some extent guide the clinician to the underlying cause, but in many cases the cause is not obvious. According to our results it here seems reasonable to test for ADH, APS-1 and DiGeorge syndrome. Antibodies against IFN-ω and NALP5 are excellent markers of APS-1 (11, 27, 28). Testing for antibodies against the CaSR among patients with idiopathic HP does not seem justified based on our results.

We believe that search for ADH among patients with idiopathic HP is important, since these should receive treatment with calcium and vitamin D only if the disease is symptomatic. The treatment increases hypercalcuria and risk of kidney failure more than other forms of HP (7). Symptomatic patients should be treated, but only to alleviate symptoms, not to restore normocalcemia, as low dosages of calcitriol results in less frequent renal calcifications (7). Diagnosis of APS-1, DiGeorge or other syndromes is also of great importance, since other components of these disorders needs to be identified and treated early to avoid untimely morbidity and mortality. Most of the patients in the Norwegian HP population received conventional calcium and active vitamin D supplementation,

which was associated with a high proportion of kidney failure, indicating need for improvement of the therapy.

Our study corroborates earlier studies showing reduced HRQoL among HP patients (29-31), especially among patients with post-surgical HP who also had significantly lower SF-36 scores than Norwegian patients with Addison's disease in six of eight dimensions and congenital adrenal hyperplasia in five of eight dimensions (32, 33). One plausible explanation could be a higher proportion of absolute PTH depletion or related to the cause of surgery, i.e. Graves' disease or thyroid cancer, but there is no correlation to the calcium levels. Receptors for PTH are found in several tissues, including the central nervous system and probably the adrenal cortex, and lack of PTH action in tissues not related to calcium homeostasis or bone metabolism may explain the reduced HRQoL. If so, PTH replacement therapy should improve HRQoL, and indeed some PTH intervention studies show convincing improvement (29, 31, 34). Neither the large placebo controlled study REPLACE nor a Danish study found such improvement (30, 35, 36), but in the Danish study many patients became hypercalcemic due to a high fixed PTH-dose. The uncertainty about effectiveness of PTH treatment may be due to dose or delivery, which so far has not restored physiological calcium homeostasis properly. Our study revealed a higher percentage of patients with clinically significant anxiety and depression than other disease groups in Norway which have been studied using HADS (37, 38). Although not directly comparable, our results are in concordance with the result from one study among 25 post-surgical HP patients (39).

The large sample size and the study design as a national study without major selection bias is the greatest strength of this study. The added inclusion criterion with need of permanent treatment for HP for more than one year for patients with post-surgical HP and HP due to DiGeorge syndrome ensured that only patients with permanent HP were included. A limitation is that even though the overall sample size is large, it constitutes a very heterogeneous group. The response rate of 55% in the patient survey should ideally have been higher, but the basic characteristics of the respondents and identified

patients were not significantly different; we therefore believe that this group is representative. Furthermore, the response among the patients who comprise the largest subgroups of the cohort (post-surgical, APS-1, ADH) were higher than for the patients within the smaller subgroups. The HRQoL data were not adjusted for age and sex, since the raw data from the normative were not available for direct comparison. However, the age and sex distributions in the patient populations were comparable to the normative population. For each age and sex stratification the trends were similar as in the overall data, but not necessarily significantly different due to small numbers in each group.

In conclusion, the prevalence of genetic, autoimmune and idiopathic HP in Norway is higher than reported elsewhere, whereas the prevalence of post-surgical HP is lower than expected. Systematic assessment of the underlying cause of HP is important to tailor the treatment, especially for patients with ADH, and to identify other syndrome components early in APS-1, DiGeorge syndrome, and HDR. Still, many patients have unknown cause. Despite conventional calcium, magnesium, and vitamin D supplementation complications such as kidney failure and reduced HRQoL are common, indicating need for improvement of the therapy.

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Table 1. Causes of hypoparathyroidism

Cause	Gene (when indicated)	Reference
Postsurgical and/or following radioactive iodine thyroid ablation		
Autoimmune		
Isolated		
Component of APS-1	*AIRE*/21q22.3	(9, 10)
Genetic		
Isolated		
ADH type 1 and 2	*CASR*/3q21.1, *GNA11*/19p13.3	(7, 40)
PTH- mutations	*PTH*/11p15	
GCMB-mutations	*GCMB*/6p24.2	(41)
X-linked recessive	*SOX3*/Xq26-27	
As part of syndromes		
DiGeorge (22q11.2-deletion syndrome)	*TBX1*/22q11	(14, 42)
HDR-syndrome	*GATA3*/10p13-14	(43)
Hypoparathyroidism-retardation-dysmorphism syndrom (Sanjad-Sakati syndrome) and Kenny-Caffey syndrome	*TBCE*/1q42.3, *FAM111*A/11q12.1*	(44-46)
Mitochondrial associated (Kearns-Sayre and others)		
Stormorken's syndrome	*STIM1*/11p15.4	(47)
Target organ resistance		
Pseudohypopara type 1 and 2	*GNAS*,*STX*/20q13.3	(48)
Blomstrand chondrodysplasia	*PTHR1*/3p22-p21.1	
Hypomagnesemia	*TRPM6*/9q21.13**	
Vitamin D dependent rickets	*VDR*/12q13.11 (type 2a)	
Idiopathic		
Miscellaneous		
Infiltrative disorders (Hemochromatosis, Thalassemia, Wilsons disease, metastasis)		

*Kenny-Caffey syndrome type 2

**Hypomagnesemia due to *TRPM6* mutations is typically accompanied by secondary hypocalcemia, but severe hypomagnesemia of any cause can give target organ resistance.

APS-1: Autoimmune polyendocrine syndrome type 1, ADH: Autosomal dominant hypocalcemia, HDR: Hypoparathyroidism, deafness and renal syndrome.

Table 2. Prevalence and cause of HP in the health regions among living patients (n=511)

	All RHA	**South-Eastern RHA**	**Western RHA**	**Central RHA**	**Northern RHA**
Inhabitants	4 985 870	2 785 259	1 041 886	687 968	470 757
HP and pseudo-HP n (prev/100000)	511 (10.2)	256 (9.2)	117 (11.2)	72 (10.5)	66 (14.0)
Post-surgical n (prev/100 000)	321 (6.4)	183 (6.6)	47 (4.5)	51 (7.4)	40 (8.5)
Non-surgical n (prev/100 000)	148 (3.0)	54 (1.9)	59 (5.7)	17 (2.5)	18 (3.8)
Idiopathic	64 (1.3)	31 (1.1)	14 (1.3)	8 (1.2)	11 (2.3)
APS-1	25 (0.5)	9 (0.3)	9 (0.9)	3 (0.4)	4 (0.8)
ADH	31 (0.6)	4 (0.1)	26 (2.5)	1 (0.1)	0
HDR	4 (0.08)	1 (0.04)	3 (0.3)	0	0
DiGeorge	23 (0.5)	8 (0.3)	7 (0.7)	5 (0.7)	3 (0.6)
Other*	1	1	0	0	0
PseudoHP (prev/100 000)	41 (0.82)	19 (0.7)	10 (1.0)	4 (0.6)	8 (1.7)
Vitamin D resistent rickets	1		1		

RHA: Regional health authorities, APS-1:Autoimmune polyendocrine syndrome type 1, ADH: Autosomal dominant hypocalcemia, HDR: Hypoparathyroidism, deafness and renal syndrome
*One with HP due to Stormorken's syndrome.

Table 3 Patients identified and survey respondents, n (%)

	Identified HP n=522	**Respondents n=283**
Age, years (range)	51 (4-91)	53 (9-89)
Female	381 (73%)	212 (75%)
Post-surgical	329 (63%)	197 (70%)
Non-surgical	152 (29%)	70 (25%)
Idiopathic	67	26
APS-1	25	15
ADH	31	18
HDR	4	1
DiGeorge	23	8
Other causes	2*	2*
Pseudo-HP	41(8%)	16 (6%)

APS-1: Autoimmune polyendocrine syndrome type 1, ADH: Autosomal dominant hypocalcemia, HDR: Hypoparathyroidism, deafness and renal syndrome.
* One with vitamin D-dependent rickets (excluded from further analysis), one with Stormorken's syndrome

Table 4 Basal characteristics, laboratory results and treatment among respondents (median- range)

	All, n=283	Surgical, n=197	Non-surgical, n=69	Pseudo-HP n=16	P-value	
Age (years), median (range)	53 (9-89)	56 (20-89)	48 (10-72)	32 (9-60)	*0.002 **<0.001	
Female n (%)	212 (75)	161 (82)	40 (58)	10 (63)	*<0.001	
BMI (kg/m^2), median (range)	25 (14-60)	25 (15-60)	25 (14-47)	25 (17-34)	NS	
Social security benefits (SSB)						
Retirement pension, n (%)	51 (18)	46 (23)	5 (7)	0	NS	
Permanent SSB, n (%)	72 (25)	53 (27)	15 (22)	4 (25)	NS	
Temporary SSB, n (%)	42 (15)	33 (17)	9 (13)	0	NS	
Laboratory results						**Ref.range/cut off**
Corrected s-calcium (mmol/L)	2.08 (1.47-2.84)	2.09 (1.61-2.69)	2.00 (1.68-2.84)	2.14 (1.47-2.25)	*0.002	2.20-2.55
s-Magnesium (mmol/L)	0.83 (0.64-1.22)	0.83 (0.64-1.22)	0.80 (0.65-1.00)	0.89 (0.69-1.10)	*0.008 ***0.02	0.71-0.94
s-Phosphorus (mmol/L)	1.29 (0.76-2.55)	1.29 (0.77-2.55)	1.32 (0.76-2.27)	1.38 (0.99-2.05)	NS	0.75-1.50[a]
TSH (mIE/L)	1.22 (0.01-14.20)	0.69 (0.01-14.20)	1.83 (0.04-5.42)	2.35 (0.01-6.86)	NS	0.40-4.50
FT4 (pmol/L)	19.3 (9.3-39.6)	20.7 (11.0-39.6)	16.6 (9.3-23.6)	15.1 (10.1-24.2)	*<0.001 **0.001	9.5-22.0
Creatinine (μmol/L)	75.0 (33-247)	76.0 (34-247)	74.0 (44-168)	60.5 (33-102)	***0.03	Male: 60-105 Female: 45-90
Estimated GFR (ml/min)	80.8 (14.6-215.7)	78.6 (14.6-181.5.)	86.3 (30.4-152.0)	105.1 (52.6-215.7)	**0.04	> 90
Urine Calcium (mmol/mmol creatinine)	0.51 (0.02-2.29)	0.53 (0.02-1.91)	0.52 (0.03-2.29)	0.17 (0.02-0.74)	**<0.001 ***0.003	0.04-0.50
Treatment, dose median (range)						**Percentage receiving treatment (all)**
Calcium mg/day	1000 (167-10000)	1000 (167-10000)	1000 (250-4000)	1000 (500-2000)	NS	70
Calcitriol µg/day	0.75 (0.13-4.00)	0.75 ((0.13-4.00)	0.60 (0.25-2.00)	1.00 (0.75-1.40)	NS	40
Alphacalcidiol µg/day	1.50 (0.25-6.00)	1.50 (0.25-6.00)	1.50 (0.40-5.00)	1.25 (0.50-4.00)	NS	44
Ergocalciferol (D_2) U/day	4286 (1286-210 000)	4286 (1286-150 000)	4286 (2143-210 000)	3214 (2143-4286)	NS	19
Cholecalciferol (D_3) U/day	800 (200-8000)	800 (200-8000)	800 (400-2400)	800 (800-800)	NS	29
Magnesium mg/day	300 (120-1200)	300 (120-1200)	300 (120-1200)	300 (120-375)	NS	34
PTH use, n	10	9	1	0		4

[a] Different reference ranges for different gender and age groups for s-phosphorus and s-creatinine. The results calculated for both sexes and all age groups combined.

*Statistical significant difference between post-surgical and non-surgical group

** Statistical significant difference between post-surgical and pseudo-HP group

*** Statistical significant difference between non-surgical and pseudo-HP group

Table 5. SF-36 and HADS score, mean (±SD) of the HP population and subgroups compared to Norwegian normative data

	SF-36								HADS			
	n	**PF**	**RP**	**BP**	**GH**	**VT**	**SF**	**RE**	**MH**	**n**	**Anxiety**	**Depression**	**Total HADS-score**
Overall													
HP & pseudo-HP	283	74.2 (24.6)	44.9 (43.8)	58.1 (26.9)	50.7 (27.2)	42.2 (22.9)	68.5 (27.3)	65.1 (42.5)	70.5 (19.5)	283	6.5 (4.4)	4.8 (4.1)	11.4 (7.7)
Normative	2311	87.2 (18.7)	77.9 (35.8)	75.1 (26.0)	76.8 (22.0)	60.0 (20.8)	85.5 (22.2)	81.6 (32.4)	78.8 (16.5)	58784	4.2 (3.3)	3.4 (3.0)	7.5 (5.5)
Females													
HP & pseudo-HP	212	72.4 (25.1)	43.1 (43.6)	56.4 (26.5)	49.3 (27.3)	40.4 (23.0)	67.6 (26.9)	66.3 (42.2)	70.0 (19.1)	212	6.7 (4.3)	4.8 (4.0)	11.5 (7.6)
Normative	1184	84.8 (20.8)	75.4 (37.7)	73.0 (26.6)	76.3 (22.5)	56.9 (21.2)	83.7 (23.1)	79.1 (34.6)	77.6 (17.0)				
Males													
HP & pseudo-HP	71	79.6 (22.0)	50.4 (44.3)	63.0 (27.5)	54.8 (26.6)	47.2 (22.2)	71.2 (28.5)	61.3 (43.4)	72.3 (20.6)	71	5.9 (4.5)	5.0 (4.7)	10.9 (8.2)
Normative	1085	89.8 (15.5)	80.5 (33.6)	77.2 (25.0)	77.4 (21.3)	63.2 (19.9)	87.6 (20.9)	84.5 (29.7)	80.0 (15.8)				
HP Subgroups													
Surgical	197	72.2 (24.4)	39.2 (43.1)	55.3 (26.0)	48.7 (27.1)	40.0 (22.6)	67.4 (27.4)	63.9 (42.8)	70.2 (19.0)	197	6.6 (4.3)	5.2 (4.0)	11.8 (7.7)
Non-surgical	69	73.5 (25.9)	58.6 (43.7)	63.8 (27.7)	52.5 (26.6)	46.4 (23.3)	71.6 (25.5)	68.7 (41.7)	71.8 (20.7)	69	6.3 (4.6)	4.0 (4.3)	10.3 (7.7)
Pseudo-HP	16	86.6 (16.4)	56.3 (39.3)	64.9 (29.5)	64.3 (26.0)	47.5 (20.5)	66.4 (32.5)	62.5 (43.7)	67.5 (22.5)	16	7.0 (4.0)	4.5 (4.6)	11.5 (8.1)

Normative data: SF-36: Loge and Kaasa (22) and HADS: HUNT databank (23). The overall SF-36 scores and the scores of post-surgical and non-surgical patients were significantly different from normative data because the confidence intervals do not overlap. The scores among pseudo-HP were significantly different from the normative scores for three dimensions (RP, VT, SF). Overall HAD scores and post-surgical HAD scores were significantly different from normative data, for non-surgical HP significantly different for anxiety and for pseudo-HP significant different for depression.

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