Hypoparathyroidism and autoimmunity in the 22q11.2 deletion syndrome

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Abstract

Objective: To characterize the endocrine and autoimmune disturbances with emphasis on parathyroid dysfunction in patients with 22q11.2 deletion syndrome (22q11.2 DS).

Design: In this nationwide survey; 59 patients (age 1–54 years) out of 86 invited with a 22q11.2 DS were recruited through all the genetic institutes in Norway.

Methods: Data was collected from blood tests, medical records, a physical examination and a semi-structured interview. We registered autoimmune diseases and measured autoantibodies, hormone levels and HLA types.

Results: Twenty-eight (47%) patients had hypoparathyroidism or a history of neonatal or transient hypocalcemia. Fifteen patients had neonatal hypocalcemia. Fourteen patients had permanent hypoparathyroidism including seven (54%) of those above age 15 years. A history of neonatal hypocalcemia did not predict later occurring hypoparathyroidism. Parathyroid hormone levels were generally low indicating a low reserve capacity. Twenty-eight patients were positive for autoantibodies. Six (10%) persons had developed an autoimmune disease, and all were females ($P<0.02$). Hypoparathyroidism correlated with autoimmune diseases ($P<0.05$), however, no antibodies were detected against the parathyroid glands.

Conclusions: Hypoparathyroidism and autoimmunity occur frequently in the 22q11.2 DS. Neonatal hypocalcemia is not associated with later development of permanent hypoparathyroidism. Hypoparathyroidism may present at any age, also in adults, and warrants regular measurement of calcium levels. Hypoparathyroidism and autoimmunity occur frequently together. Our findings of autoimmune diseases in 10% of the patients highlight the importance of stringent screening and follow-up routines.

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Introduction

In 1965, DiGeorge (1) described three neonates with severe immunodeficiency, thymus aplasia, and neonatal hypocalcemia due to aplasia of the parathyroid glands. Later, cardiac anomalies were added to the phenotype called DiGeorge syndrome. In 1992, it was discovered that the majority of these patients had a microdeletion on chromosome 22q11.2 (2). This is now recognized as the most common microdeletion syndrome in humans with an incidence of $\sim$1:4000 live births (3).

Hypoparathyroidism in the 22q11.2 deletion syndrome (22q11.2 DS) patients is often transient and resolves after the neonatal period, but may manifest itself later in life as episodes of hypocalcemia during stress such as infectious disease, surgery or pregnancy. In some patients permanent hypoparathyroidism develops (4–6). There is limited knowledge about the pathogenesis and natural course of hypoparathyroidism, but a developmental defect may explain why the parathyroid glands are small and have limited capacity of parathyroid hormone (PTH) production (7). Alternatively, an autoimmune destruction or inhibition of function could also be operational, since individuals with the 22q11.2 DS are prone to autoimmune diseases (8, 9), particularly cytopenias (10–12), juvenile idiopathic arthritis (8), and celiac disease (13). One study reported autoimmune disorders or detectable autoantibodies in 33% of the patients (9).

Patients with 22q11.2 DS have an immune defect caused by thymic hypoplasia. Thymic T cell diversity (14) and output is reduced (15) with reduced absolute
numbers of naïve CD3CD45RA (15) and regulatory CD3CD4CD25 T cells (16). B cells can also be affected (17) with a tendency for immunoglobulin deficiencies (18–20). These alterations are not severe, but could at least partly explain an increased frequency of autoimmune disorders.

Autoimmunity against the parathyroid is rare and reports are scarce. Moreover, both blocking and stimulating antibodies against the calcium sensing receptor have been reported (21, 22), the latter giving rise to hypoparathyroidism. Recently, a novel parathyroid autoantigen NACHT leucine-rich-repeat protein 5 (NALP5) was reported in patients with autoimmune polyendocrine syndrome type 1 (APS1) (23). Whether these autoantibodies are involved in DiGeorge syndrome is not known.

The aim of this investigation was to conduct a nationwide study on endocrine and autoimmune disturbances in patients with 22q11.2 DS, with special emphasis on parathyroid dysfunction.

Patients and methods

Patients

Through the genetic institutions in Norway, 86 patients diagnosed with a 22q11.2 DS by fluorescent in situ hybridization (FISH) from 1993 to 2006, were invited to participate in a nationwide survey (24). Sixty-two patients agreed to participate, two dropped out before the study started due to medical reasons. One patient who refused blood testing was included in the clinical part only. Fifty-nine patients, 31 females and 28 males, median age 9 years (range 1–54), from all parts of Norway were included. The diagnosis was verified using a multiplex ligation-dependent probe amplification assay (24). All patients were observed at the Pediatric Outpatient Clinic at Rikshospitalet, Oslo University Hospital between 2005 and 2007. The study was approved by the Regional Committee for Research Ethics and the Norwegian Data Inspectorate. Before inclusion, written informed consent was obtained from the participants or their parents.

Clinical data

By using a semi-structured interview and scrutinizing the medical records we identified neonatal hypocalcemia (from birth to 1 month of age) and later hospitalizations due to hypocalcemia. Hypoparathyroidism was defined as S-calcium below the reference range with inappropriately low PTH concentration. Since hypocalcemia is the most potent stimulus of PTH secretion; a low or even normal serum PTH concentration in a patient with hypocalcemia is a strong evidence of hypoparathyroidism (25) in the presence of elevated phosphate levels and the absence of kidney failure. Celiac disease was verified by duodenal biopsies.

Autoimmune and related diseases were registered based on typical biochemical findings and clinical evaluation.

Clinical chemistry

We measured the levels of total calcium (2.15–2.55 mmol/l; Elecsys Modular PE, Roche), ionized Calcium (1.14–1.32 mmol/l; ABL, radiometer, Diadem Diagnostics, Holliston, MA, USA), intact PTH (Immulate 2000, Luminometer, Siemens, Munich, Germany), 25-hydroxyvitamin D (37–131 nmol/l), and 1,25-dihydroxyvitamin D (72–216 pmol/l in children, 42–169 pmol/l in adults; competitive RIA, DiaSorin, Stillwater, MN, USA). Other hormone measurements were: TSH, free thyroxine (Modular PE, Roche), IGF1 (Immulate 2000, Luminometer), IGF binding protein 3 (IGFBP3; ELISA, Diagnostic System Laboratories, TX, USA), ACTH (Berilux analyzer 250, B.R.A.M.H.S. Diagnostica GmbH, Berlin, Germany, luminometer chemoluminescence immunoassay), cortisol, LH, FSH, and estradiol/testosterone (Modular PE, Roche). Immunoglobulins were measured and compared with age-related standards (26). DRB1 and DQB1 genotyping was performed with a PCR-based sequence-specific oligonucleotide probe system at four-digit resolution as described elsewhere (27). The DQA1 alleles and HLA-DRB1-DQA1-DQB1 haplotypes were deduced based on known patterns of linkage disequilibrium in the Norwegian population. Exon 3 was not typed, and so we did not distinguish DQB1*0201 from *0202.

Antibody assays

Autoantibodies against organ-specific autoantigens: 21-hydroxylase (21OH; <48), 17z-hydroxylase (17OH; <102), side-chain cleavage enzyme (SCC; <184), glutamic acid decarboxylase 65 (<122), tryptophan hydroxylase (<84), tyrosine hydroxylase (TH; <103), protein tyrosine phosphatase (<77), NALP5 (23), aromatic l-amino acid decarboxylase (<89), and interferon ω (<200) were measured using RIA based on the proteins expressed by in vitro transcription and translation (28, 29). We also measured antibodies against: nucleus (anti-nuclear antibodies (ANA), indirect immunofluorescence (IIF); <32) performed on a human epithelial-2 cell substrate, and if positive ANA against double-stranded DNA (ELISA); anti-smooth muscle (ASM; <20), mitochondria (IIF, <20); parietal cells (IIF, pos 1:20); thyroid peroxidase (TPO, a modified ELISA; 1–99 IU/ml); islet cells antibodies (IIF, <4); intrinsic factor (0.0–5.9 U/ml); thyroglobulin (Tg) (ELISA) (1–99 IU/ml); tissue transglutaminase (IgA, ELISA; 0.0–4.9 U/ml), and thyroid-stimulating antibodies (TSAb; 1.0–2.0 IU/l), and rheumatoid factor (RF; latex IgA) an antibody against the Fc portion of IgG (1–8 AU/ml).
Statistical analysis

SPSS for Windows release 14.0 (Chicago, IL, USA) was used for the statistical descriptive analyses of the data. Data are expressed as median (range). We used t-test for (log transformed) PTH levels versus the (log transformed) reference values. To evaluate possible differences in frequency of autoimmune diseases in patients with or without hypoparathyroidism χ² tests with Yates correction were performed. We also used χ² tests to look at differences in frequency of autoantibodies detected in patients with and without hypoparathyroidism and presence of neonatal hypocalcemia versus later occurring hypoparathyroidism.

Results

Neonatal hypocalcemia

The patients’ main clinical features are summarized in Table 1 and have also been reported elsewhere (15, 24). Neonatal hypocalcemia was registered in the medical records of 15 of 59 patients (25%). Blood tests had been taken due to symptoms such as quivering, convulsions, or hypotonia in nine patients or as a routine check in six patients with suspected 22q11.2 DS due to cardiac anomalies (Table 2). Two of the 15 patients had permanent hypocalcemia, three reverted to normocalcemia, but hypoparathyroidism occurred at ages 2, 10, and 26 years respectively. The remaining ten patients had no further registered episode of hypocalcemia from birth to the study examination.

Hypoparathyroidism

Fourteen of the 59 patients (24%) had hypoparathyroidism at examination including five of the patients with neonatal hypocalcemia described earlier (two permanent and three recurrent; Table 2). One had experienced an earlier episode of transient hypocalcemia during cardiac surgery before permanent hypoparathyroidism was diagnosed. In addition, four other patients had

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aThe age in years at the start of hypocalcemia or hypoparathyroidism is given in parenthesis.

bDiagnosed in this study.
experienced one or more episodes of hypocalcemia during surgery, infection or follow-up. The classification of transient or permanent hypoparathyroidism proved difficult in one patient (no. 11, Table 2) because calcium and vitamin D supplementation was started quickly after hypocalcemia was discovered.

Altogether 28 (47%) patients had neonatal, transient or permanent hypocalcemia at some point during follow-up (Table 2). Seven (54%) of 13 patients above 15 years of age had hypoparathyroidism. The occurrence of hypoparathyroidism after the age of 15 was independent of the occurrence of neonatal hypocalcemia (P > 0.2).

The PTH levels at examination were generally low (Fig. 1) with a median value of 2.3 pmol/l (range <0.6–6.4) compared with the reference values (P < 0.001). Fourteen (24%) patients had PTH below the lower reference value, 57 (97%) patients were in the lower half of the reference interval or below, demonstrating that the PTH production is impaired in these patients. The PTH levels tended to decline with increasing age (data not shown).

The median serum calcium concentration was 2.32 mmol/l (range 1.85–2.56 mmol/l), leaving most patients within the normal range, indicating that treatment with calcium supplements alone or combination with vitamin D was adequate.

Vitamin D levels were measured in 55 patients. All had 1,25-dihydroxyvitamin D in the normal range. Six patients had low levels of 25-hydroxyvitamin D, of whom five were normocalcemic and one hypocalcemic.

**Autoimmune and related clinical diseases**

Six patients (10%) had autoimmune diseases (Table 3), all were females (P < 0.02). Two patients had celiac disease, diagnosed at age 6 and 11 years, three had hypothyroidism diagnosed at 20, 22, and 26 years of age (Table 3), and one was also diagnosed with pernicious anemia and atrophic gastritis. Finally, one patient had idiopathic thrombocytopenic purpura at age 6 years and seronegative arthritis at age 15, diagnosed as psoriatic arthritis. These latter four patients also suffered from hypoparathyroidism that was significantly more frequent in patients with autoimmune disease than in those without (P < 0.05). In addition, one other patient had severe psoriasis, one had Raynaud phenomenon, and two had asthma.

**Growth and hormone deficiencies**

Eight patients (14%) had a birth weight below the 2.5th percentile and 12 (20%) below the 5th percentile according to gestational age using Norwegian standards (30). Seventeen (29%) of the patients were below the 2.5th percentile of height. Only one adult patient had low levels of IGF1 and IGFBP3 compared with age references. No patients had low cortisol and high ACTH or elevated HbA1c and none of the patients had hypogonadism. We did not diagnose any new cases with hypothyroidism.

**Autoantibodies, immunoglobulins, and HLA**

Sera from 28 (48%) of the 58 patients analyzed had detectable autoantibodies against a wide range of autoantigens (Table 3). However, no serum showed positivity for antibodies against NALP5, a parathyroid autoantigen. Most sera displayed low antibody indices. The most frequent autoantibodies were ASM (n = 7), TH (n = 7), and ANA (n = 6). In the ANA-positive group, two patients aged 5 and 8 years, had high titers (2560 and 512). None had antibodies against DNA. We also found autoantibodies against endocrine glands. In particular, the steroidogenic enzymes 21OH, 17OH, and SCC were targeted in nine patients (Table 3). Five of the patients with autoantibodies to 21OH also had autoantibodies against one or two other adrenal enzymes. All these patients had normal ACTH and cortisol levels.

Antibodies against TPO were less abundant and found in two of three patients with hypothyroidism. The patient without anti-TPO and hypothyroidism had the diagnosis for 16 years. Anti-Tg was positive in four patients; three of whom had normal thyroid function. There was no difference in autoantibody frequency in patients with or without hypoparathyroidism.

One 10-year-old patient had IgA deficiency. The patients with celiac disease all had the associated HLA DRB1*03-DQB1*02 haplotype. The patients with other
autoimmune manifestations did not demonstrate any clear associations to HLA haplotypes normally associated with these disorders in the Norwegian population (data not shown). However, the limited number of patients with evidence of autoimmunity does not allow for any firm conclusions to the role of HLA genotypes.

### Discussion

We have conducted a broad nationwide cross-sectional study of 59 patients with 22q11.2 DS to characterize endocrine and autoimmune disturbances with emphasis on parathyroid dysfunction. We actively invited all patients in Norway with a diagnosis of 22q11.2 deletion confirmed by FISH to participate, taking advantage of the relatively small and surveyable population of the country. Our cohort is probably representative for the diagnosed Norwegian 22q11.2 DS patient population, but there is an uncertainty related to the fact that 26 diagnosed cases did not participate for unknown reasons. However, with an estimated incidence of 1:4000, a considerable number of patients remain to be identified, just as for other published 22q11.2 DS cohorts. Some of the seriously affected individuals included in this study were diagnosed late, indicating that the phenotypic variation is also great among the undiagnosed individuals. Other reported studies may be biased since they originate from specialized clinics (9, 18).

Forty-seven percent of the patients had hypoparathyroidism or a history of neonatal or transient hypocalcemia. There is a great variety in the clinical presentation and severity of hypocalcemia and hypoparathyroidism in our patients. Neonatal hypocalcemia is one of the cardinal symptoms of DiGeorge syndrome, however, its prevalence in 22q11.2 DS is difficult to establish. Our patients were only tested when they had symptoms of hypocalcemia or clinical suspicion of the syndrome. Thus, the occurrence of neonatal hypocalcemia may be underestimated. Still, it is probable that the patients with most pronounced hypocalcemia developed symptoms and were tested. This is supported by documented normal calcium levels in three neonates.
tested due to quivering. To establish the overall prevalence of neonatal hypocalcemia, systematic screening is required.

There is little, reported follow-up data about the association between neonatal hypocalcemia and later parathyroid gland function in these patients. In one previous report of 61 patients with 22q11.2 DS 20 of them had neonatal and five developed permanent hypoparathyroidism from birth (31). In our study, only two patients had permanent hypoparathyroidism from birth. In total five of 15 patients with neonatal hypocalcemia got later permanent hypoparathyroidism versus nine of 44 patients without neonatal hypocalcemia. There was no significant association, even in those neonates with severe symptoms in the neonatal period (Table 2). Therefore the occurrence of neonatal hypocalcemia could not predict later permanent hypoparathyroidism.

Hypoparathyroidism can be diagnosed at all ages in patients with 22q11.2 DS, and 54% of the patients above 15 years had hypoparathyroidism (Table 2). In our study, four adult patients were diagnosed with 22q11.2 DS due to hypoparathyroidism (24). We demonstrate that hypoparathyroidism can be diagnosed at all ages in patients with 22q11.2 DS. Mild hypocalcemia without symptoms may last for many years. This is also reflected in the low levels of PTH (Fig. 1) indicating that the PTH reserve is limited in the 22q11.2 DS. Consequently, patients should be screened for hypocalcemia at regular intervals to prevent symptoms and complications to hypocalcemia, and 22q11.2 DS should always be considered as a cause of hypoparathyroidism in persons without a history of thyroid surgery.

Studies have shown an association between immunodeficiency syndromes in childhood and the later development of autoimmune disorders (32). IgA deficiency, the most common primary immunodeficiency with a prevalence of 1 per 500–700 among Europeans, is associated with both systemic and organ-specific autoimmune diseases (33). The prevalence of IgA deficiency in our study was one of 59 in contrast to one of eight in two previous reports (9, 18), which might be influenced by their selection of patients.

We found autoantibodies in 28 patients (47%) especially ANA, which is even higher than in an earlier report on autoimmunity in 22q11.2 DS (9). Only two patients aged 5 and 8 years, had high titers (2560 and 512) of ANA, and none had anti-DNA. This is in contrast to absence of ANA or RF after thymectomy during cardiac operations in non-syndromic infants (34). Most of the patients had ANA and ASM in very low titers. The prevalence of positive ANA among healthy individuals varies depending on age and sex and is reported in 30–40% of blood donors (35). Children with positive ANA and without clinical signs of an autoimmune disease have been found to have a minimal risk of developing an autoimmune disease despite the persistently positive ANA (36). Only follow-up studies can reveal if ANA or ASM positivity is an early marker of autoimmune disease in 22q11.2 DS patients.

We also detected autoantibodies against enzymes in the adrenal gland in sera from nine patients. This is of particular interest, as APS1 (37) and 22q11.2 syndrome both have defects in thymic function. All patients with adrenal autoantibodies had normal ACTH and cortisol levels, and the autoantibody indices were lower than observed in most patients with primary autoimmune adrenal insufficiency (38) or APS1. Among relatives of patients with an organ-specific autoimmune disease the presence of autoantibodies against the adrenal gland predicts developing autoimmune adrenal disease (39). The high frequency of low titers of autoantibodies (Table 3) may indicate an impaired immune system in the 22q11.2 DS patients (15).

An autoimmune disease was found in six patients (10%), of whom four in addition suffered from permanent hypoparathyroidism. This association reaches statistical significance (P < 0.05), but patient numbers are low. There are few studies including adult 22q11.2 DS patients, and our data indicate the importance of including screening for autoimmunity when planning follow-up routines. Hypothyroidism was diagnosed in three adult patients (Table 2). In addition, one patient had positive TSAb, but no hyperthyroidism. Autoimmune thyroid disease found in three of ten (30%) patients above the age of 17 years is a slightly higher incidence than in a previous report of 78 adult 22q11 DS patients (40) and also higher than in the general population in Norway (5%) (41). Two patients had celiac disease, diagnosed at age 6 and 11 years. This is more frequent than in an earlier report (13) and may warrant screening of celiac disease in 22q11.2 DS patients. We found one patient with idiopathic thrombocytopenic purpura and seronegative arthritis, diagnosed to be psoriatic arthritis, in contrast to earlier studies reporting increased prevalence of juvenile idiopathic arthritis (42). These results warrant a study on a much larger population of patients with 22q11.2 DS since many different autoimmune diseases may occur.

The pathogenesis of the reduced parathyroid capacity could be an autoimmune destruction or congenital hypoplasia that becomes evident as the demand for PTH secreting capacity increases with age. None of the 22q11.2 DS patients had parathyroid (NALP5) antibodies, but this does not exclude a low-grade ongoing autoimmune process without detectable antibodies, since NALP5 so far has been shown to be a marker for autoimmune hypoparathyroidism in APS1 patients only. A recent report finds an association between hypoparathyroidism and clinically significant T cell immunodeficiency in the 22q11.2 DS (43). We have earlier reported on the thymic function of 43 of the patients (15). Only one had clinically significant tendency to serious infections when tested. However, our study is too small for any conclusions to be made on
a possible connection between low thymic output and autoimmunity disease or hypoparathyroidism. Also, age is a confounding factor since the prevalence of autoimmunity and hypoparathyroidism increases and thymic function declines with increasing age.

It was expected that the same class II major histocompatibility complex susceptibility genes that confer risk for multiple autoimmune diseases in the general population might be more frequent in 22q11.2 DS patients with an autoimmune manifestation. Sullivan et al. (42) found HLA alleles associated with higher risk of juvenile idiopathic arthritis in three of three 22q11.2 DS patients. However, the limited number of patients with evidence of autoimmunity does not allow for any firm conclusions to the role of HLA genotypes. We failed to show a correlation between HLA alleles and autoimmunity, but we cannot exclude the possibility due to a lack of statistical power.

In conclusion, hypoparathyroidism and autoimmunity occur frequently in the 22q11.2 DS. Neonatal hypocalcemia is not associated with later development of permanent hypoparathyroidism. Hypoparathyroidism may be transient or permanent and occur at any age. Our findings highlight the importance of stringent screening and follow-up routines of these patients. Hypoparathyroidism and autoimmunity occur frequently together. A high frequency of adrenocorticoid bodies was detected, but evidence of a specific autoimmune response against the thymus was not found.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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