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ORIGINAL PAPER

Age-dependent clinical problems in a Norwegian national survey of patients with the 22q11.2 deletion syndrome

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Abstract Patients with the 22q11.2 deletion syndrome display a wide phenotypic variation that is important for clinical follow-up. In this national survey of 60 patients (ages 1 to 54 years) diagnosed by Fluorescence in situ hybridization test, data were collected from medical records, a physical examination, and a semistructured interview. Ultrasound investigation of the kidneys was also performed. In addition, multiplex ligation probe amplification assay was performed to detect deletion size. Phenotypic features leading to the genetic diagnosis were noted. The patients showed a variety of organ malformations including 39 with heart anomalies. Only 20 individuals had been diagnosed with 22q11.2 DS in the first year of life. Four patients had renal and five males had genital malformations. The increased infection susceptibility (excluding otitis media) and most feeding difficulties subsided during early childhood. Speech difficulties started early and were a major problem for many patients at least until 10 years of age. Ten patients developed kyphoscoliosis in late childhood. In teenagers and adults, abnormal social behavior, learning disabilities, and psychiatric symptoms dominated. Our study which also includes adult patients emphasizes a marked change in challenges in individuals with the 22q11.2 deletion syndrome with increasing age.

Keywords 22q11.2 deletion syndrome · DiGeorge syndrome · Velocardiofacial syndrome · Congenital cardiac anomalies

Abbreviations

ADHD	Attention-deficit hyperactivity disorder
22q11.2 DS	22q11.2 deletion syndrome
CTCA	Conotruncal cardiac anomaly
FISH test	Fluorescence in situ hybridization test
MLPA	Multiplex ligation probe amplification
PEG	Percutaneous endoscopic gastrostomy
VPI	Velopharyngeal insufficiency
VSD	Ventricular septum defect

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Introduction

The 22q11.2 deletion syndrome (22q11.2 DS) is the most common microdeletion syndrome in humans, with a

reported incidence of approximately 1:4,000 live births [5, 11, 24]. The phenotypic variation is large, and the most frequent clinical findings are: cardiac malformations, thymic hypoplasia, velopharyngeal insufficiency, feeding difficulties, hypoparathyroidism, immunodeficiency with recurrent infections, and learning difficulties [25]. In Norway, this syndrome has been diagnosed using fluorescence in situ hybridization (FISH) test since 1993 [9]. This assay detects 95% of such deletions. The inheritance of 22q11.2 DS is autosomal dominant, though 85–90% of deletions appear to be de novo [6, 8]. New molecular approaches have increased our understanding of the mechanisms underlying the genomic rearrangements responsible for 22q11.2 DS. The deletion appears to be linked to a region with at least eight discrete blocks of low copy number repeats called A–H [1, 4, 28]. This region is one of the most rearrangement-prone sites in the human genome, resulting in deletions and duplications during gametogenesis. Most individuals have a deletion size of 3 megabase pairs (Mb) although 8% have a 1.5-Mb deletion and 2% have smaller atypical deletions. Recently, a new diagnostic tool, a multiplex ligation probe amplification (MLPA) assay, has been developed to detect copy number changes of genes in this region [14] to delineate the size of the deletions or duplications. The gene for Tbx1, a transcription factor, is always included in the deletion, and Tbx1 mutations have also been identified in humans having the clinical phenotype [35]. This gene is essential for neural crest function, and cell fate mapping has linked it to the development of the heart, the parathyroid glands, the brain, and the sclerotome (a structure which develops into the spinal column) [17]. Studies prior to the introduction of the FISH test almost 20 years ago had to rely solely on the characteristic signs and symptoms for the diagnosis of the syndrome. The availability of genetic testing revealed that velocardiofacial and DiGeorge syndromes were due to the same 22q11.2 deletion [27]. Consequently, there is sparse information available on adult patients with a diagnosis confirmed by genetic testing. Two large surveys, one from Europe [26] and one from USA [7], were published just after the introduction of the FISH test, and a more recent Swedish study has also been published [23]. In the later years, the awareness of the heterogeneity of this syndrome has substantially increased among physicians. This has led to the identification of a growing number of older individuals with the 22q11.2DS without cardiac anomalies. In addition, an increasing number of patients with psychiatric problems have been reported [2, 20, 34].

We have performed a population-based study of the clinical phenotype of the 22q11.2 deletion patients in Norway. Our main aim was to characterize the clinical problems in different age groups.

Materials and methods

Patients diagnosed between 1993 and 2006 using commercially available FISH probes were recruited for this study through the genetic institutions in Norway. Invitation letters were sent to 86 patients or to their parents of which 62 (71%) consented to participate, two dropped out before the study started due to medical reasons. The study was approved by the Regional Committee for Research Ethics and the Norwegian Data Inspectorate. A written informed consent was obtained from either the patient (age >18 years), the parents (patient age <12 years), or both patients and parents (patient age 12–18 years). All participants were seen at the Outpatient Clinic of the Division of Paediatrics at Rikshospitalet University Hospital between 2005 and 2007. One of the authors (KL) performed both a routine physical examination of the patients and a semistructured interview with all the patients or parents. The interview emphasized the following issues: birth weight and length of pregnancy; cardiac anomalies; feeding issues including breast feeding, ingestion process with possible nasal regurgitation, and later percutaneous endoscopic gastrostomy; speech problems and learning difficulties including the need for extra support in kindergarten or school; sleep disturbances; and the use of medications. Finally, every participant or parent was asked to define the main problem at present and for the reason for genetic testing. The data obtained in the interview were checked with the medical records of the patients. Reports from echocardiography, cardiac catheterization, and radiographs were also consulted. Data on cleft lip and palate were obtained from surgery records.

Ultrasound of the kidneys was performed with an ATL HDI 5000 sonographic scanner. The examinations were performed by two experienced radiologists. MLPA was performed using SALSA MLPA kit P 250 A1 DiGeorge, from MCR-Holland to test the 22q11.2 region for deletions or duplications in 57 patients where sufficient DNA was available.

Statistical analysis

SPSS for Windows release 14.0 (Chicago, IL, USA) was used for the statistical descriptive analyses of the data, including a Chi-square test for correlations between various phenotypic features. Data are expressed as a median (range).

Results

Sixty patients, 32 females and 28 males, with a median age of 9 years (range 1–54) having a FISH confirmed 22q11.2 deletion, were included in this study. Fifty-three of these were sporadic cases. In addition, seven patients were

recruited from four families, a father and his two sons, a mother and her daughter, and two fathers, where index children did not participate. According to the MLPA results, 53 of 57 patients showed the large A–D deletion, three had the smaller A–B deletion, and one patient an A–C deletion. None of the participants had duplication in this region. There was no observed relationship between deletion size and clinical symptoms.

Phenotypic features leading to genetic diagnosis

All 20 (33%) patients who had received a 22q11.2 DS diagnosis before 12 months of age had a congenital cardiac anomaly (Fig. 1). These patients had conotruncal cardiac anomalies (CTCA) typical for 22q11.2 DS, and in 12 cases, the surgeon could not locate the thymus gland intra-operatively. In addition, two participants had hypocalcemia and two had the characteristic facial appearance of the syndrome. In 40 (67%) patients who received a genetic diagnosis after 12 months of age, we identified the following reasons for performing a FISH test. In three participants, this was due to the recognition of characteristic facial features. Only two participants were tested as a consequence of frequent infections. Seven patients with a typical CTCA were diagnosed retrospectively including three patients born before 1993. Two of these had no visible thymus at cardiac surgery. The rest had feeding difficulties, typical facial features, or learning disabilities in addition to their cardiac anomaly. Fifteen patients were FISH tested due to speech problems or a submucous cleft palate, and six of them had an additional cardiac anomaly in their medical history. Only two patients were diagnosed due to learning disabilities, and two patients had miscellaneous features. Five patients were tested because of a positive family history, two fathers, one mother, and two children. In total, eight adults (18–51 years at diagnosis) were included, five of which were discovered due to clinical problems such as hypoparathyroidism.

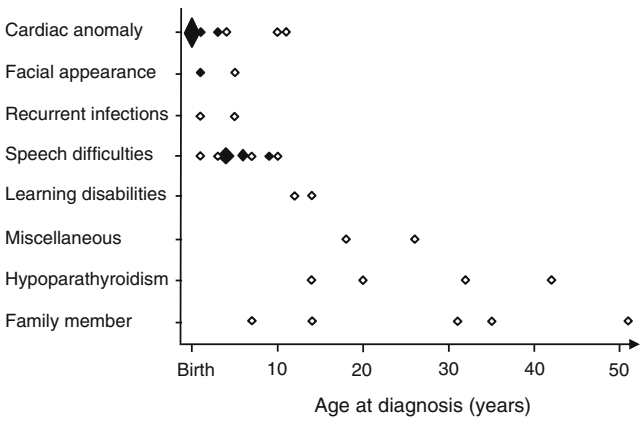

Fig. 1 The main phenotypic feature leading to the positive FISH-test versus age at diagnosis. The *symbols* represent: one patient (◇), two (◆), four (◆), five (◆), and 20 patients (◆). Median age at diagnose 4 years, range 0–51 years. Miscellaneous features: one patient with a muscular VSD, overt cleft palate, hernias, and recurrent infections and one patient with developmental delay, mental retardation, scoliosis, and transient neonatal hypocalcemia

Neonatal period

Data of birth weight and gestational age were available for 55 patients. The median birth weight was 3,020 g (1,200–4,325 g), and the median gestational age was 40 weeks (31–42 weeks). Ten (17%) were born prematurely at weeks 28–36. Eight patients (13%) had a birth weight below the 2.5th percentile and 12 (20%) below the 5th percentile according to gestational age using Norwegian standards [30]. Severe cardiac defects were discovered in the postnatal period. Eleven patients with interrupted aortic arch and one patient with pulmonary atresia were operated on within 10 days after birth due to severe hemodynamic problems. Oropharyngeal problems such as feeding difficulties started commonly from birth with poor suckling. At least 36 (60%) patients had problems with regurgitation of fluid/milk through the nose. Nevertheless, 32 (53%) patients were breastfed for 3 weeks to 3.5 years. This information lacked in three adults. At birth, six (10%) infants had an isolated overt cleft in the soft palate, and only one of them had a cleft in the hard palate. Various other malformations were discovered. Four had pes equino varus or plano valgus, and three had polydactyly of the hand or foot. Five (18%) of the male patients had genital deformities: undescended testis (two patients), phimosis (two patients), and hypospadia (one patient). Furthermore, one girl had an extra mamilla.

In infancy

Twenty-six of the 39 patients with a cardiac anomaly (Table 1) had cardiac surgery during the first year of life, while nine were operated later. During the first year, oropharyngeal problems continued, and 38 (68%) babies had trouble with swallowing. One or more hernias appeared in 24 (40%) of the patients, 16 had an umbilical hernia, two had a ventral hernia, and 12 had an inguinal hernia.

Early childhood

The feeding difficulties were complex and continual. Three (5%) patients needed PEG for a certain period. Furthermore, 41 (68%) patients disclosed velopharyngeal insufficiency (VPI), excluding two patients that had not been evaluated, another two that were too small to be examined, and one patient where the diagnosis was uncertain.

Table 1 Cardiovascular anomalies and frequency of conotruncal defects

Cardiac anomalies	Number of cases	Percentage	Additional defects (*n*)
Interrupted aortic arch + VSD	12	(31)	ASD (6)
Tetralogy of Fallot	4	(10)	
Pulmonary atresia + VSD	6	(15)	MAPCA (3)
Double right ventricle outlet	1	(3)	Doubly committed VSD + hemitruncus
VSD (membranous/subpulmonal)	12	(31)	PS (2), AAA (2), PDA (1) or AC (1)
VSD (muscular)[a]	1	(3)	
ASD[a]	3	(7)	
Total	39	(100)	
Conotruncal origin[b]	35	(90)	

[a] Non-conotruncal cardiac anomalies

[b] Total minus non-conotruncal anomalies

AAA aortic arch anomalies, *AC* aortic coarctation, *ASD* atrial septum defect, *MAPCA* major aorto-pulmonary collateral arteries, *PDA* percistent ductus arteriosus, *PS* pulmonary stenosis, *VSD* ventricular septum defect

Fourteen patients had surgery for submucous cleft palate or VPI at a median age of 6.2 (4.8–11.6) years reflecting that the child must be able to cooperate to evaluate this problem. Forty-nine (82%) patients had speech difficulties related to VPI and speech delay resulting in an evaluation by a speech therapist. According to their parents, at least 19 (32%) patients communicated using signs before they started to speak. Only eight of the patients had no speech difficulties. Also, three patients had an autism spectrum disorder. Twenty-seven (45%) patients received extra support in kindergarten such as speech therapy and guidance of social behavior. Four patients postponed the start of school for 1 year. Forty-seven (78%) of the patients reported recurrent infections, defined as three or more episodes in 1 year (Table 2), this being almost exclusively otitis media and pneumonia. Twenty-six participants underwent a tympanostomy tube insertion. In 37 of the children, the susceptibility to infections disappeared at a median age of 4 years and in most patients before 7 years of age. Serious viral infections were not seen. Many of the patients had hypotonia with pes planus. Twenty-two (37%) patients had overlying toes, most often the second toe.

Late childhood

In school, all but one adult needed a learning support assistant or a special-needs teacher in mathematics and reading. Attention deficit/hyperactivity disorder was diagnosed and treated in three patients. Thirty-one (52%) of the patients had some kind of sleep disturbance, most frequently sleep onset delay, and 12 patients (20%) used *N*-acetyl-5-methoxytryptamine (Melatonin®). In eight patients, susceptibility to infections diminished between 6 and 7 years of age. Ten of 31 (32%) patients older than 7 years had frequent infections, either recurrent otitis media (seven patients) or one to two episodes of pneumonia per year (three patients). Ten of 42 (24%) patients older than 6 years developed scoliosis (nine patients) or kyphosis (one patient).

Adolescence and adulthood

In secondary school, all patients required individual learning plans including special-needs teachers and one-on-one or small-group teaching. Five patients stated

Table 2 Characteristics of infections until 7 years of age

Infection frequency	Number of cases	Percentage	Localization of infection	Number of cases
Recurrent (more than 3 episodes annually)	47	(78)	Otitis media	31
			Pneumonias	15
			Fever episodes	1
Few (less than 3 episodes annually)	9	(15)	Common cold	6
			Sore throat	2
			Pneumonias	1
None	4	(7)		

depressive mood during adolescence, and two adults complained of anxiety. One adult had schizophrenia, and one had pathological compulsive actions. Two of seven patients older than 24 years held an ordinary job.

Ultrasound studies of the kidneys

Ultrasound examination of the kidneys identified four (6.7%) patients with anomalies; one with a single kidney, one with hydronephrosis and stenosis of the ureter, one with isolated hydronephrosis, and one with a cyst in one kidney. In addition, three patients had nephrocalcinosis probably due to excessive calcium and vitamin D supplementation as treatment for hypoparathyroidism.

Main problem reported by the patient/parents

Table 3 lists the prominent problems reported by patients or parents in their own words. Only two patients reported that the heart defect or symptoms related to the cardiac anomaly was the issue most worrying for them. The patients and their parents stated that speech problems started early but gradually diminished with increasing age or after velopharyngeal surgery. In older patients, fewer problems related to organic malformations such as cardiac anomalies or cleft palate affecting feeding and speech and more problems with issues such as attention and social behavior were reported. The youngest children had trouble with reciprocal social interaction such as following rules of games, while older children had more problems with social relations such as making friends. Concentration deficits started in kindergarten and were the most prominent problem at school. In adults, psychiatric disorders predominated. Only two patients indicated no major problems, one child and one adult.

Discussion

The variable clinical phenotype of the 22q11.2 DS involving multiple organ systems is a diagnostic challenge. It has become evident from our population-based study which included adults up to 54 years of age that many clinical features are characteristic at certain ages. The general trend of the symptomatology was a change from medical problems in early childhood to social–emotional functioning in adolescence ending with psychiatric problems in the adult patients. There is a limited number of adults with 22q11DS to study, because FISH tests have only been available since 1993, and adult patients have mainly social and psychiatric problems previously not warranting this diagnostic test. 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 and the universal healthcare system of the country. Thus, our data are

Table 3 Age-related main problems defined by the patients/parents

Age (years)	Number of cases	Main problems
1–2	7	Speech problems
		Recurrent infections
		Feeding difficulties
3–5	11	Speech problems
		Social behavior
		Concentration deficit
		Feeding difficulties
		Cardiac problems
6–10	18	Social behavior
		Concentration deficit and learning disabilities
		Speech problems
11–15	12	Concentration deficit and schoolwork
		Social relations
		Depressive mood
		Hypotonia
16–25	6	Learning disabilities
		Psychiatric problems
		Social relations
26–54	6	Psychiatric diseases
		Social relations
		Money matters

probably representative for the diagnosed Norwegian 22q11DS patient population. However, with an estimated 22q11.2 DS incidence of 1:4,000 [5], it can be calculated that in the Norwegian population of about five million, a high number of patients have not yet been identified.

Notably, all the 20 patients diagnosed within 12 months of life had a conotruncal cardiac anomaly (CTCA). This represented only half of the patients with a cardiac anomaly, although 90% of the patients had a CTCA typical for this syndrome. Only two of 12 patients with a peri-membranous VSD located in the conotruncal part of the heart received the 22q11.2 DS diagnosis before the age of 1 year. A symptom that could suggest the diagnosis early is feeding difficulties. However, none of our patients were diagnosed due to feeding problems, and half of the infants were breastfed, including one with an overt cleft palate and 10 that later were operated for submucous cleft palate or VPI. Breastfeeding is important for many reasons including a possible stimulation of thymus growth and function [12, 13]. Feeding problems were complex and needed various age-related treatment approaches, but these were transient in most patients.

Speech-related problems started early and were a major problem for many patients at least until 10 years of age. In our study, 49 (82%) patients had difficulties due to VPI and/or speech delay. Many of our patients used manual signs to enhance communication. This is also reported by others [31]. In 15 of our patients, speech difficulties led to genetic testing (Fig. 1). The submucous cleft palate and the VPI are difficult to discover in early childhood since the diagnosis depends on cooperation with the child. Accordingly, these patients were diagnosed later. Six patients (10%) in our study had overt cleft palate. The reported prevalence of 22q11.2 DS with this defect is only 1.8% but increases to 30% if the patient also has a cardiac anomaly [29]. The impaired and delayed ability to communicate with others and the speech difficulties due to VPI might result in social withdrawal and poor social skills in these children and adolescents [33].

In early childhood, 47 (78%) of our patients had recurrent infections, usually otitis media. This tendency was transient and not as severe as reported by others [10, 16, 23]. We have defined recurrent infections as more than three episodes annually. The patients were only mildly immunodeficient (manuscript in preparation) and did not experience opportunistic infections. Otitis media in these patients may be due to anatomical deviations and functional impairment of the pharynx and ear rather than to a compromised activity of the immune system. Later on, immunodeficiency may contribute to the increased autoimmunity described in this patient group (manuscript in preparation) [10, 16], as seen in patients with other primary immunodeficiency diseases [18].

In the first surveys of 22q11.2 DS, a high number of renal anomalies (36%) were reported [26]. This was not confirmed in our study (6.7%). We found 18% genital anomalies in male participants; this corresponded with the results of the Swedish study [23]. The scoliosis in these patients typically appears in late childhood or adolescence [19]. In our study, 10 (24%) of the patients had developed scoliosis and/or kyphosis after 6 years of age. This proportion is higher than in other studies [19, 23], probably because our study population was older.

At school age, most of our patients utilized educational supports. Other researchers have shown that these patients' IQ scores are lower than normal and that they have a mild developmental delay [3, 20, 34]. Patients are also often described as having an attention-deficit disorder [21, 32] that may influence their learning capacity. In our study, only three patients had an ADHD diagnosis, although many had problems with attention in school. This is in accordance with the experience that children with reduced/low intellectual level often have some attention deficit without meeting the full criteria for ADHD [22]. In addition, patients with 22q11.2DS often have an inattention type of ADHD, which is not easy to diagnose [21]. However, while 20% of participants in the Swedish study were identified due to learning disability [23], this was the case for only two (3%) of our patients. Sleep problems were widespread among our patients, in the same way as reported for patients with other neurodevelopmental disabilities [15].

Our study design has a limitation related to the recall assessment in the interview with the patients or parents. To diminish this possible recall bias, we have checked available data in the medical records for confirmation.

Conclusion

In this national survey, we studied patients along the age spectrum to learn more about the natural history of the 22q11.2 DS. The various phenotypic features typically appear in a chronologic manner. First, the organ malformations dominate, and later, neuropsychological problems appear. Medical problems such as scoliosis in adolescence and psychiatric disorders in adults may develop. It is important that healthcare providers are aware of the changing face of clinical challenges for these patients over the life course in order to organize an optimal lifelong follow-up for the patients with 22q11.2 DS.

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