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Early speech and language development in children with 22q11 deletion syndrome

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Introduction

22q11.2 deletion syndrome (22q11DS) is a relatively frequently occurring syndrome; the population prevalence is estimated between 1:2000- 1:4,000 births (Shprintzen, 2008). It is thought that many cases, especially those with mild symptoms, remain undiagnosed. It is not uncommon that when parents of children diagnosed with 22q11DS are tested, they are also found to have the syndrome. Consequently, it is not unlikely that 22q11DS is systematically underdiagnosed. It has even been suggested that the incidence of 22q11DS might approximate the incidence of Down syndrome, which is 1:1000 (Solot et al., 2000). 22q11DS has many eponyms, which is probably the result of the highly variable expression in individuals. Names that are often used for this syndrome are velo-cardio-facial syndrome (VCFS, named after the most common symptoms of the syndrome), DiGeorge syndrome, and Shprintzen-syndrome (after the ENT-specialist dr. R.J. Shprintzen and his colleagues, who were the first to describe the syndrome (Shprintzen et al., 1987)). In this thesis, the term 22q11.2 deletion syndrome will be used, as this reflects its basic etiology: affected individuals have a micro-deletion on the long arm of chromosome 22, at band q11.2. This means that individuals with 22q11DS have only one copy of the genes lying within the band 22q11, while typically one would have two copies, one from the paternal allele and one from the maternal allele.

22q11DS is easily detected using modern DNA-diagnostic techniques. Most affected individuals (85-90%) have similar deletions of 3 million base pairs (= 3 megabase, 3Mb), but a small proportion (about 10-12%) have smaller deletions of 1.5 or 2 megabases (Shaikh et al. 2000, see figure 1). The three megabase deletion

encompasses a region containing approximately 30-40 genes (Shprintzen, 2008; Shaikh et al. 2000). In most cases (~90%), the 22q11 deletion is 'de novo', which means that neither parent of the child has the 22q11 deletion. However, the syndrome is hereditary, and passes on from parent to child in an autosomal dominant pattern, which means there is a 50% chance that a person with 22q11DS passes the deletion on to his or her child. Boys and girls are equally affected.

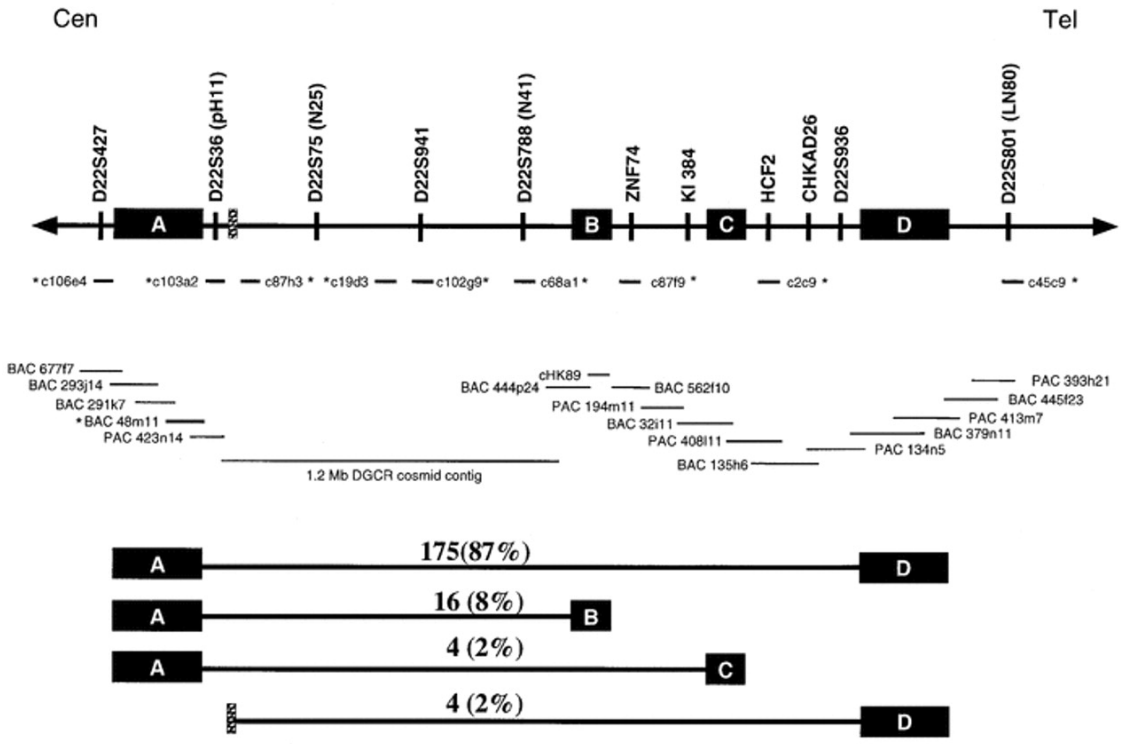

Figure 1. LCR-A, -B, -C and –D are indicated as filled boxes. The percentages above the lines which indicate deletion size (at the bottom of the figure) represent the percentage of patients identified with these deletion boundaries.

Reprinted from Shaikh, T.H, Kurahashi, H., Saitta, S.C., Mizrahy O'Hare, A., Hu, P., Roe, B.A. et al. (2000) Chromosome 22-specific low copy repeats and the 22q11.2 deletion syndrome: genomic organization and deletion endpoint analysis. *Human Molecular Genetics*, 2000, Vol. 9, No. 4: 489-501.

Phenotypical characteristics

22q11DS has an expansive phenotype: more than 180 clinical features have been associated with the syndrome. Symptoms can both be physical and behavioral, and can have impact on nearly every organ system and (developmental) function. No single clinical feature occurs in 100% of cases and there is no reported case that has all or even most of the clinical features. The diagnosis is therefore defined by the deletion of DNA from chromosome 22 at band q11.2 (Shprintzen, 2008).

Frequently occurring clinical features are congenital heart disease (especially conotruncal heart anomalies, interrupted aortic arch type B, tetralogy of Fallot, truncus arteriosus, and ventricular septal defects) and palatal anomalies (mostly cleft palate and (occult) submucous cleft palate). Velopharyngeal insufficiency (VPI), which means that the soft palate cannot fully close the nasal cavity, is almost invariably seen. The result of VPI is that air is allowed to escape through the nose instead of the mouth during speaking, resulting in speech sounding nasally.

Children with 22q11DS often show some characteristic facial features, such as a long face, asymmetric crying face, 'hooded eyelids', a broad nose tip, and almond shaped eyes. Furthermore, it is often noticed that their fingers are rather long and tapered.

Apart from these physical characteristics, cognitive, behavioral and psychiatric characteristics can be observed. The cognitive level of children with 22q11DS is often a borderline range of functioning (Full Scale IQ 70-75). Research has shown however that IQ in children with 22q11DS is not stable. Duijff et al (2012) performed a longitudinal study regarding the cognitive development of children at the ages of 5.5, 7.5 and 9,5. They found a mean decline of 9.7 IQ-points between the ages of 5.5 and 9.5, and found that the decline in the verbal scale was twice as large as the decline on the performance scale. This could partially be explained by 'growing into deficit', which means that children do develop when they are growing older, but not at the same rate as their typically developing peers

are. But there was also a group of children showing an absolute decline in raw score development.

Attentional deficits are often observed and children with 22q11DS are at an increased risk of various psychiatric disorders such as Autism Spectrum Disorders (ASD), Attention Deficit/Hyperactivity Disorder (ADHD), various anxiety disorders and psychotic disorders. During adolescence and early adulthood, up to 30% of patients develop schizophrenia (compared to about 1% in the general population). Another common clinical feature of 22q11DS that is often mentioned is speech-language impairment. (Shprintzen, 2008)

Research on speech and language development in children with 22q11DS

Although clinicians agree that speech and language disorders are present in the majority of children with 22q11DS, research into the exact nature of these problems has been limited.

Golding-Kushner, Weller & Shprintzen (1985) were the first to describe a pattern of language disorders and personality characteristics of children with 22q11DS. The researchers conducted a retrospective study involving 26 patients with 22q11DS in New York, divided over three age groups (ten children younger than 6 years, ten children between the age of 6 and 11, and six children older than 11 years of age). They used a wide range of psychometric tests to evaluate for speech and language (Wide range Achievement Test (WRAT), Peabody Picture Vocabulary Test (PPVT), the Illinois Test of Psychometric Abilities (ITPA) and the Detroit Tests of Learning Aptitude), observation and formal IQ-tests (Stanford-Binet Intelligence Scale and Leitner International Performance Scale for children younger than 7 years; Wechsler Intelligence Scale for Children-Revised (WISC-R) for older children), and reviewed school records and interviewed parents. All children had hypernasal speech. Most parents of the children felt that speech onset was delayed, but in most cases they could not remember when specific milestones were reached. With respect to vocabulary, children below 6 years had a 'borderline normal' score, children between 6 and 11 years old were 'severely delayed' and

children older than 11 showed an increase compared to the children between 6 and 11. The data were not compared with the data of typically developing peers. Both VIQ and PIQ seemed to decrease with increasing age. A qualitative impression of the language use of the children younger than 6 years was a poor responsiveness to simple questions, a preference for non-verbal communication (even if there speech intelligibility was good), reduced utterance length and little structural complexity. Children older than 11 years showed a reduced expressive vocabulary, an immature grammar and limited abstract reasoning, but did have functional communication ability.

Scherer, d'Antonio & Kalbfleish (1999) described the speech and language development of four children with 22q11DS, two of them had a cleft palate, one a submucous cleft and a deep pharynx and one only had a deep pharynx. It is unclear how these children were selected. Two of the four children grew up in intact families with parents that were not affected, the other two children lived in extended families with their mothers who were affected and with maternal grandparents that were not affected. The authors studied them longitudinally from 6 months to 30 months of age, and compared their development with three groups of children: typically developing children, children with cleft lip and palate (CLP) and children with an isolated cleft palate (ICP). Scherer et al. state that there are some similarities in the speech of children with 22q11DS and children with cleft lip and/or palate, including VPI and the use of compensatory speech sounds (e.g. glottal stops). However, the authors argue that the developmental profile of speech and language impairments in children with 22q11DS is different from that of the control groups. Their data indicated that the children with 22q11DS had severe receptive-expressive language impairments from a very early stage of language development, and these impairments increased in severity from 12 to 30 months of age. Both early vocabulary and speech sound acquisition were severely impaired to the extent that the children were practically non-oral up to 30 months of age. A marked discrepancy between receptive and expressive language and speech production could be observed. The development of speech and expressive language was more severely delayed than would be expected based on their receptive language abilities and their development in other areas.

Solot et al. (2000) aimed to provide a description of the communicative and developmental features in a sample of children with 22q11DS. The purpose of their paper was to familiarize speech and language pathologists with the syndrome and its characteristics. The paper describes some of the findings in the areas of speech, language, and hearing in a cohort of patients at The Children's Hospital of Philadelphia (CHOP) and The Children's Seashore House of CHOP (CSH). At the time of the study, 305 children with the 22q11DS had been enrolled in a prospective study at CSH of CHOP. However, the results in their report are based on different sub-groups of the larger cohort. It does not always become clear how many children were evaluated in a subgroup for a specific aspect. For evaluation of speech and language, the following measures were used: Pre-School Language Scale-3, Clinical Evaluation of Language Fundamentals-Revised, Goldman-Fristoe Test of Articulation, Peabody Picture Vocabulary Test-Revised, Expressive One Word Vocabulary Test-Revised. The authors found that in a sample of 31 children 5 years of age and older, 77% had articulation disorders and only 23% were within normal limits. These problems were considered to be the result of palatal abnormalities or VPI. However, the authors also mention that many children presented with motor speech disorders, like dysarthria and dyspraxia. Another aspect of speech that often occurred in the children was hypernasality. Solot et al. mention that most children in the cohort showed language delays, also if they did not give evidence of any cognitive deficits. Almost all children were delayed in the emergence of language milestones. They found that 69% of 40 children were not yet speaking at the age of 24 months, or had just a few words or signs. In all children who had no speech by 2 years of age, expressive language was delayed beyond what was expected given their cognitive levels. Significant differences were found between receptive and expressive language in preschool children, with more severe delays observed in expressive language. In children below 4 years of age, expressive language was delayed to a greater extent than other developmental skills. A distribution of disabilities was found in school aged children that was quite similar to that seen in preschool children. There was a downward shift of IQ scores. The authors argue that speech and language delays are characteristic for the syndrome. Language emergence is often delayed until the age of 2 to 3 years. As soon as language emerges, some children show improvement maturationally,

whereas for others delays in development continue through the preschool years. This delay cannot be explained by cognitive factors alone and suggests the presence of specific (in this context uses as being 'not secondary to cognitive delay') speech and language impairment in many children.

Glaser et al. (2002) tried to define a language profile for children with 22q11DS and wanted to explore if the parental origin of the deletion had any influence on the language abilities of the child. 27 children with 22q11DS ('VCFS-group', 19 male, 8 female, ranging in age from 6 to 19 years) were matched for sex, age and IQ with 27 children with idiopathic developmental delay ('DD-group'). 54 typically developing children (siblings of children with fragile X-syndrome genetically identified as normal) were used as a control group. Parental origin of the deletion was confirmed for 21 of the children (12 had a deletion on the allele of maternal origin, 9 on the allele of paternal origin) with 22q11DS, in all these children the mutation proved to be 'de novo', which means that none of the parents had 22q11DS themselves. The subjects were tested with the Clinical Evaluation of Language Fundamentals-III (CELF-III), which consists of different subtests (concepts and directions, word classes, semantic reasoning, formulated sentences, recalling sentences, and sentence assembly) and leads to a score for receptive language, a score for expressive language and a total language score. Remarkably, Glaser et al. reported that the receptive language skills of the children with 22q11DS were significantly lower than the expressive language skills. According to the researchers this is a unique finding when compared with the IQ-matched control group. These results also contradict the results of the studies of Scherer et al. (1999) and Solot et al. (2000), discussed above, where results for receptive language in the children with 22q11DS were better than for expressive language. Glaser et al. suggest that when the children grow older, their expressive language abilities grow better, while their receptive language abilities reach a plateau. Children with a deletion of paternal origin scored higher on both expressive ($F=3.82$, $\delta f= 19$, $P = .065$) and receptive language ($F=5.85$, $\delta f= 19$, $P = .026$) when compared to children with a deletion of maternal origin, but the difference only reached statistical significance for receptive language. Glaser et al.

state that this finding suggests 'an effect of imprinting on the regions of the brain associated with language abilities'[1].

Persson et al. (2006) investigated the ability to retell a narrative, the phonology, syntax and receptive vocabulary in 19 Swedish-speaking children with 22q11DS between the ages of 4;11 and 8;5. They used the Bus Story-test, in which children have to retell a story. This test is considered a sensitive indicator of higher-level language and cognitive skills. Based on the information content, the length of the sentences and the grammatical structures used, the age level for receptive and expressive oral language of the children can be assessed. All but two of the children had an information score of 1 SD below the population mean. There was a negative correlation between age and the information score, which implied that the older the children were, the more severe the problems were. Their ability had not deteriorated, but they had probably not progressed as fast as would be expected according to age norms. Almost all children produced shorter sentences than expected according to the population mean. Furthermore, low grammatical complexity (measured as the number of subordinate clauses compared with the mean for age) was found in about 75% of the subjects. Even though sentence length and grammatical complexity were reduced, a relatively low prevalence of grammatical errors was found. 7.7% of the utterances included grammatical errors, most common errors being errors of prepositions, gender, definite article and incomplete utterance. About 50% of the patients had a complete consonant inventory, while most typically developing children have a complete sound system at the age of 4. The authors state that this means that the phonological process analysis implies a delayed, but not necessarily a deviant, development. An exception are glottal stop errors related to velopharyngeal impairment (VPI). The group had a moderately low score for receptive vocabulary. The authors point out that limitations in receptive vocabulary have consequences for the results for other areas, especially for expressive language. If a child does not understand the Bus Story Test well, he or she will not be able to adequately retell the story. No

1 Imprinting refers to the fact that some genes are expressed only on paternally transmitted chromosomes and others are expressed only on maternally transmitted chromosomes (Jorde, 2010).

differences related to gender were found on any of the variables. Persson and her colleagues conclude that language difficulties in all investigated areas of language were found, and they suggest that speech-language impairment is a common feature of 22q11DS. The results indicate a lower result on information score in the Bus Story test and on receptive vocabulary than expected according to PIQ. Persson et al. mention that the phenotype is characterized by cognitive problems, attention deficit and social interaction difficulties. All these symptoms will probably have an influence on the language outcome. The authors state that whether or not a specific speech and language profile exists for the 22q11DS population is one of many questions that remains unanswered, although the results of the study do point in the direction of a distinctive communication profile for children with 22q11DS.

Based on research discussed above, a distinctive profile regarding speech and language development in children with 22q11DS seems to become clear. The majority of the children seem to have a delayed phonological development. Furthermore, their speech is often hypernasal. The children speak their first words often at a very late age (> 2 years), receptive language seems to be better than expressive language (although Glaser et al. found the opposite in older children) and sentences tend to be short and have a very simple structure.

Thus, speech and language problems are accepted to be a common clinical feature in children with 22q11DS. However, research in this area has been quite limited. Often, language development was investigated as part of a more elaborate study regarding the cognitive development of these children. A lot of different tests are used and it is not always clear if these tests actually measure the data the researchers want to obtain. For example, as a measure of language performance, in many cases verbal IQ (VIQ) is used. Although VIQ is a useful measure to get an impression of the verbal competence of a child, it does not only measure linguistic abilities, but also other psychological aspects, like reasoning (antonyms, sequential order of events). It is therefore difficult to make a clear distinction between purely linguistic factors and other factors that contribute to the results of these tests. As a result, the validity of VIQ as a measure for language development can be disputed.

Furthermore, samples of children examined are often small (e.g. four children in the case of Scherer et al., 1999), or are limited to a very specific age group (6 to 30 months (Scherer et al., 1999) or 5- to 8-years old children (Persson et al., 2006)). The four children that were selected by Scherer et al. all had clefts and it does not become clear how the selection procedure was done. It is unclear how to generalize these results to all children with 22q11DS, both with and without a cleft. Two of the four children studied by Scherer lived with a mother who was also affected, which may have affected the linguistic environment in which the child was raised.

The results of studies discussed above are (partly) inconsistent: Scherer et al. (1999) and Solot et al. (2000) state that the problems with expressive language are greater than the problems with receptive language, but the results of Glaser et al. (2002) contradict this.

Research questions and methodology of this thesis

Background

As discussed above, speech and language problems are accepted to be a common clinical feature in children with 22q11DS. More specific research regarding early language development in children with 22q11DS would facilitate an early diagnosis, early language intervention and maybe a prognosis of language outcomes at a later stage in life. Early language intervention could possibly affect language outcomes later in life in a positive way.

Research questions

The main aim of this pilot study is to obtain a better insight/perspective in/on speech and language development in children with 22q11DS. A qualitative, retrospective, multiple case survey was performed using the medical files of children with 22q11DS between the ages of 0 and 8-10 years old and their language development. The main research question is: What are the characteristics of the speech and language development (that is in phonology, semantics, syntax and pragmatics) in children with 22q11DS between the ages of 0 and 8-10, and in what way is this different than in typically developing children of that age group? Additional research questions are: What can be said about the clinical,

psychological and genetic background of these children in relation to language development? Are there any suggestions for treatment based on the outcomes?

22q11DS Expertise Centre - Utrecht Medical Centre

For this multiple case study, data were used that were available from the 22q11DS Expertise Centre of the Wilhelmina Children's Hospital (WKZ), University Medical Centre Utrecht, which houses an outpatient clinic for children with 22q11DS. This 22q11DS -outpatient clinic was established in 2007, with the objective to provide the best possible care for children with 22q11DS. In this outpatient clinic, children are seen by a multidisciplinary team, consisting of, among others, paediatricians, plastic surgeons, ENT-specialists, psychiatrists, psychologists, geneticists and speech language therapists/pathologists. The aim of this multidisciplinary team is to check for possible 22q11DS-associated developmental problems and to design a comprehensive treatment plan. The large variation in nature and severity of the symptoms in 22q11DS demands multidisciplinary diagnostic process and treatment. Early recognition of possible physical and developmental problems in various areas is essential for optimal care.

Selection of cases

All studied cases were children from a Dutch-speaking environment who were genetically confirmed with 22q11DS. All children who visited the WKZ '22q11DS-outpatient clinic' in the years 2008, 2009 and 2010, and who at the time of this visit were not older than 4;0 (the age at which children in The Netherlands typically start elementary school) were selected. Consequently, at the moment the data were studied (second half of 2014), the age range of the children was 4 to 8-10 years, and data was available for a period of at least four years. This means that within the sample data were available for a developmental period from about 0 to 8-10 years of age. This will give a good impression of the development these children have made during these critical years for language and speech development. As the survey is based on medical files of the children, the data is less susceptible to parental memory flaws. The actual information at that time is available. Based on the selection criteria discussed above, 34 children were included in this study.

Case studies

For the case studies, the files available at the 22q11DS expertise centre of the WKZ were used. As this study is based on documentation already available, and no personal details of the children would be published, no further approval by a medical ethical committee was necessary.

The files of the children were reviewed and the correspondence and reports within the files were analyzed for different aspects of speech language acquisition: speech, phonology, vocabulary and semantics, morphology and syntax, pragmatics and story telling. The reports and correspondence studied were mainly derived from ENT physicians, paediatricians, clinical geneticists, plastic surgeons, speech language therapists, psychologists, psychiatrists and physiotherapists, and cardiologists.

In the case studies, I have tried to give an overview of the language development of the children and the aspects that might be relevant to this development. I have looked at:

Speech and language characteristics

- Were language and speech tests performed, and if so, what were the results?
- Is the child experiencing any problems in the field of speech and language, and if so, which areas of language are affected (phonological, semantic, syntactic, pragmatics), and what are the characteristics of these problems?
- Can anything be said about non-verbal communication?

Cleft/Velopharyngeal insufficiency (VPI)

- Does the child have velopharyngeal insufficiency?
- Does the child have a cleft palate?
- Was the child operated for the cleft and if so, at what age?
- Are there any other anatomical anomalies?

Psychological background

- What is known about the cognitive level of the children?
- Are there any other psychometrical test results (e.g. mathematics, short term memory, processing speed)?

Genetic profile

- What type of deletion does the child have? What is the size of the deletion?

Other

- Are there any hearing problems?
- What other physical problems does the child have?
- Are there any other factors that could be influencing the speech language development of the children?

Results

Subjects

In the present study, the files of 34 Dutch-speaking children (18 girls, 16 boys), diagnosed with 22q11DS were reviewed. A full listing of the characteristics of the participants can be found in the appendix.

Characteristics of the subjects

Cleft/Velopharyngeal insufficiency

Although the name 'Velocardiofacial syndrome' is sometimes used for 22q11DS, and refers to symptoms often seen in these children (clefts, cardiological problems and specific facial features) not every child with 22q11DS actually has a cleft. In fact, only 6 of the 34 children studied had a cleft palate.

In the medical files, the speech and language problems are often connected to the presence of a cleft, although the children without a cleft experienced the same problems in speech language development. Velopharyngeal insufficiency (VPI), caused by a palate that is too short, hypotone muscles and dysfunction of the velum, seems to play a much more prominent role.

14/34 (41%) of children underwent surgery for VPI (some even several operations), but in many cases the improvement in speech was unsatisfactory.

Psychological background

Although almost all children of whom data was available score below average on IQ-tests, only few children are considered "mentally disabled"(5 children had an IQ < 70). In many cases, children attend regular elementary schools, most with extra help for language.

Figure 2 shows the IQ-ranges that were found for the 34 children reviewed for this paper.

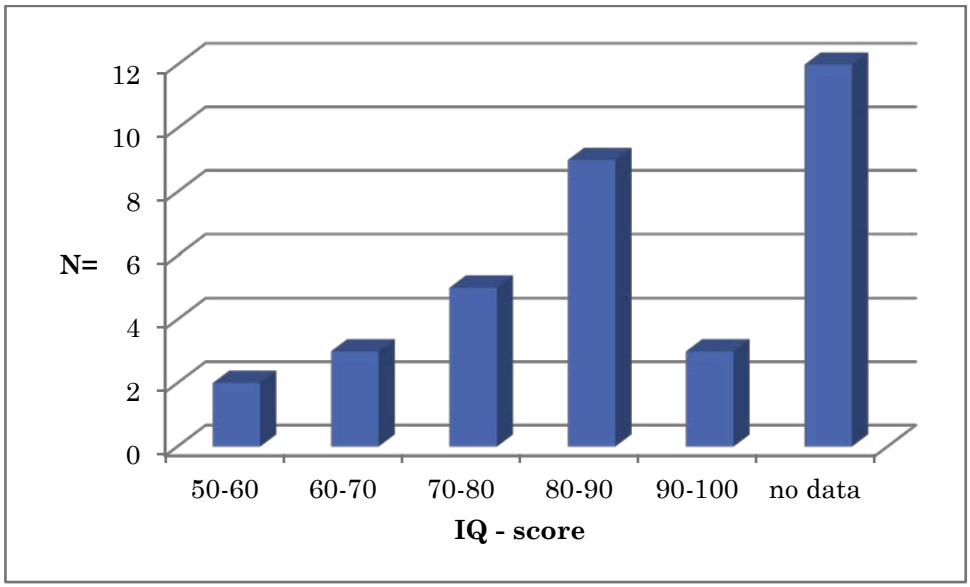

Figure 2. Results for total IQ

Other pyschological characteristics

Four out of 34 children were diagnosed with Autism Spectrum Disorder (ASD). These children were the same children that showed difficulties in pragmatical aspects of language, like turn taking and judgment of the knowledge of the listener.

Many of the 34 children were reported to have problems regarding concentration. Often, it was necessary to test them at more than one moment, because it was not possible to finish the test because of a loss of concentration on part of the child.

Genetic profile

Not all files mention the genetic profile of the children. For 15 of the 34 children (44%) specific information on the exact size of the deletion in the 22q11-

region was available. Ten of the children for whom data were available, had the 'classic' deletion of approximately 3 Mb between low copy repeats (LCR) A and D. This deletion encompasses the genes CLTCL1, HIRA, CDC45L,CLDN5, GP1BB, TBX1, TXNRD2, DGCR8, ZNF74, KLHL22, PCQAP, SNAP29 and LZTR1. Two children had a slightly smaller deletion of about 2.8 mB between LCR A and D, and one child had a deletion of 2.5 mB between LCR A and D. In one case, the child (child 22) had a larger deletion of approximately 4 Mb, between LCR A and E. Of specific interest is that there is one girl (child 31) who does not show particular problems in speech and language development. This girl has a smaller, non-classical deletion in the 22q11-region, of about 1.5 Mb, between LCR C and E.

Most deletions were 'de novo'. In one case the mother was tested after the child was diagnosed with 22q11DS, and was also diagnosed with 22q11DS.

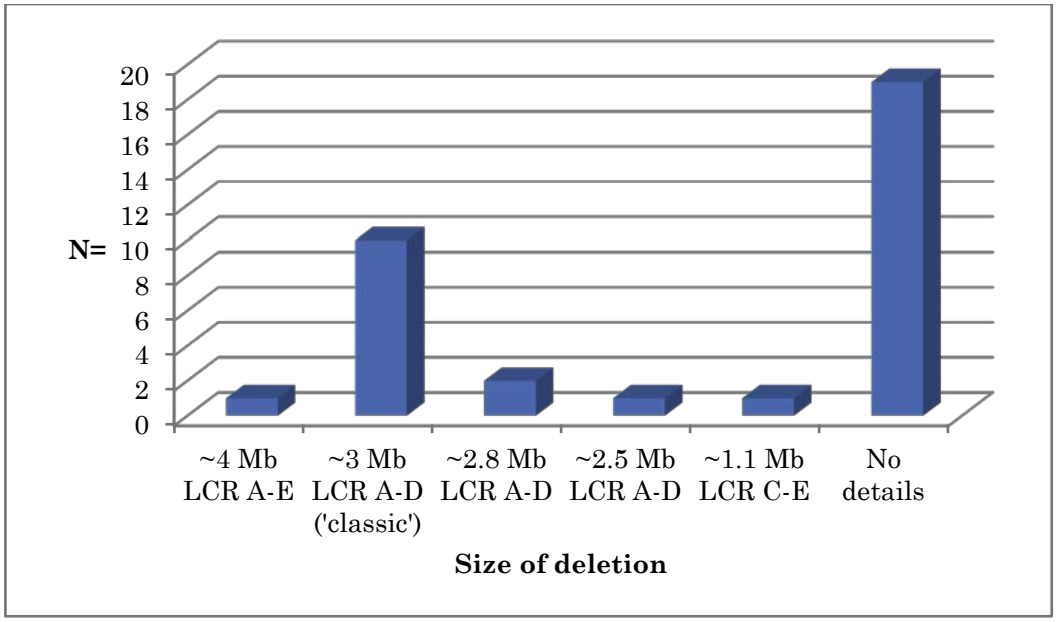

Figure 3. Types of deletion in 22q11-region

Hearing

Ten children (29%) suffered from hearing loss, in most cases conductive. Four of these children had a hearing loss of -40 to -60dB, and used hearing aids to compensate. Two children had a hearing loss of -25 to -30 dB. One child was wearing a hearing aid for this, for the other child it did not become clear from the file if the child was wearing a hearing aid or not. The other children had a hearing

loss of about -/- 15 dB on both sides. The majority of children suffered from frequent otitis media.

Interesting enough, it is specifically mentioned for four of the children that they show a hypersensitivity for loud sounds. Even though they need hearing aids for understanding speech, they habitually covered their ears when exposed to noise.

Other physical problems

20 of the 34 children (59%) have cardiac problems, mainly consisting of conotruncal heart anomalies, tetralogy of Fallot and ventricular septal defects.

Many cases of respiratory tract infections and immune problems were reported. Frequently children were admitted to hospital because of serious respiratory tract infections.

A total of 21 children showed nasal resurgitation or dysphagia (in one case this seemed to be a complication of cardiac surgery), which seemed to be related to velopharyngeal insufficiency and a hypotone oral musculature, and were treated for eating problems related to this.

Seven of the children were referred to a child neurologist because of epileptiform seizures, but in no case abnormalities were found after neurologic examination.

Speech language therapy

Almost all children were seen by a speech language therapist at some point in time. Early therapy was mostly directed at swallowing and feeding problems. Later on, therapy was mainly directed at problems in speech, which are apparent at a very early stage. To a much lesser extent attention was paid during speech language therapy to problems in language development.

Speech and language characteristics

Speech/phonology

Problems in speech production of children with 22q11DS are usually noticed at an early stage. These problems are most likely caused by velopharyngeal insufficiency (VPI), and to a lesser extent by a cleft palate (in 6 of the 34 children a cleft palate/submucous cleft was seen, another child was suspected to have a submucous cleft, but this could not be determined with certainty). 20 of the 34 children showed (severe) hypernasal resonance, mostly caused by a palate that was too short, a malfunctioning velum and/or weakness of the muscles in the oropharyngeal area.

Furthermore, 13 children could not achieve enough intraoral pressure to adequately produce plosive and fricative sounds. Speech was often characterized by nasal emission, omission of consonants and compensational strategies like backing, glottal reinforcement and consonant cluster reduction[2].

Most children's speech was reportedly very difficult to understand. In many cases, even the parents needed context to be able to understand their child. School-aged children often were told by their peers that they "talked funny", and were sometimes hesitant to speak because of this.

2 The phenomenon of 'backing' occurs when a child substitutes a sound that should be made in the front part of the mouth with a sound that is produced further back in the mouth. For example, a /b/ is substituted with a /g/, and the child says /gun/ instead of /bun/. In glottal reinforcement, a glottal explosive is uttered almost exactly at the same time as an oral explosive. This phenomenon occurs in many varieties of English, but is not very common in Dutch. Cluster reduction occurs when one or more consonants in a cluster of consonants is omitted, the child would say /tes/ instead of /test/ for example.

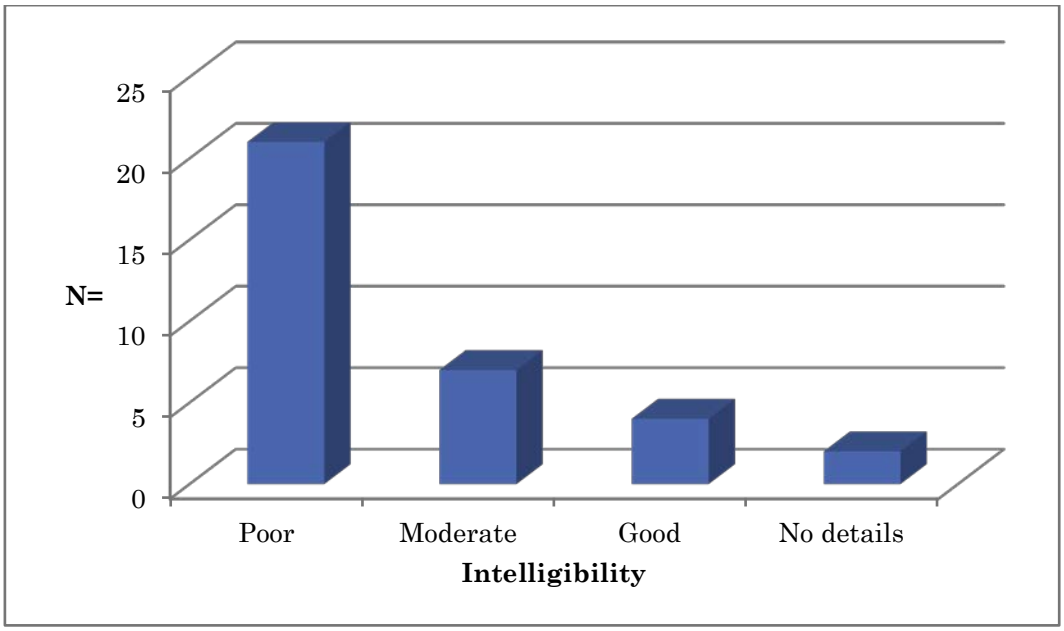

Figure 4 Intelligibility (as evaluated by parents and speech language therapists)

Babbling

For five young children it was noticed that they had never babbled and did not use speech when they were playing by themselves. Four other children had started to babble at a rather late age (ranging between 0;10 and 2;10 (years;months).

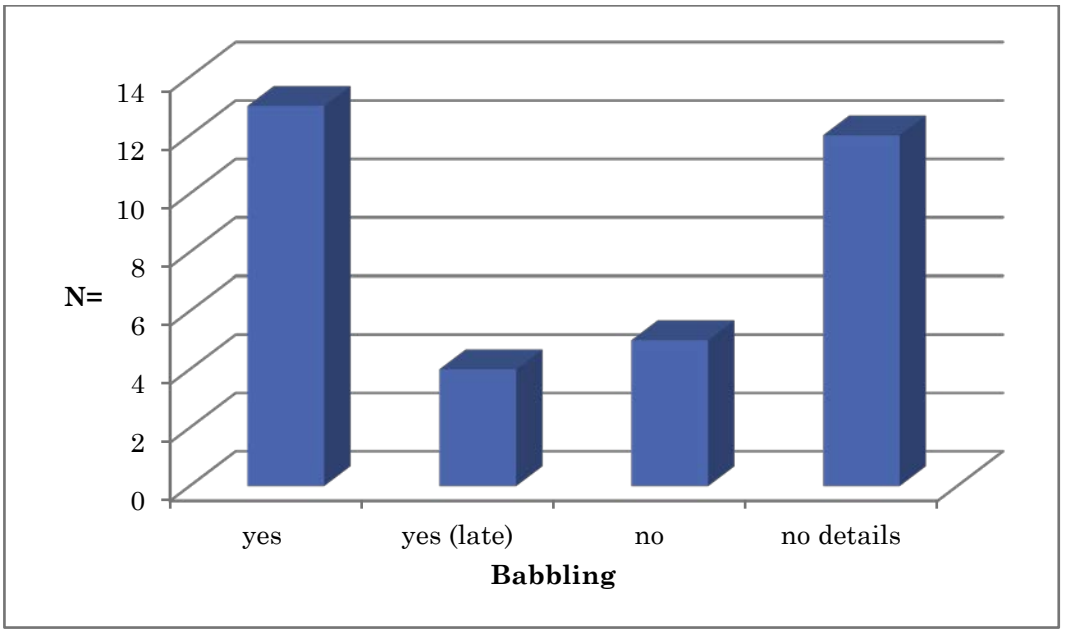

Figure 5. Results for babbling

Onset of talking and early syntax (2-3 word sentences)

For analysis of the results of vocabulary and early syntax, I used the parameters for language development as set in the 'Van Wiechen criteria' (Van Wiechen-Ontwikkelingsonderzoek, 2005). This list with 75 cognitive and motor-parameters is often used by paediatricians in the Netherlands to evaluate the cognitive-motor development in children during the first years of their lives. It states the ages at which 90% of all children have reached a specific developmental milestone. The 10% of the children who have not reached the milestone by that time should be seen by a physician to evaluate if they might have a disorder (this is not necessarily the case).

I have used the following parameters from the Van Wiechen-schedule:

- Parameter 37: 90% of the children will have a productive vocabulary of at least 2 words by the age of 15 months
- Parameter 41: 90% of the children will be able to combine 2 words in a short sentence by the age of 2 years
- Parameter 45: 90% of the children will be able to combine 3 words in a sentence by the age of 3 years

The results are summarized in table 1. A more elaborate overview for first words and early syntax per child can be found in the appendix.

Tabel 1 Overview first words and early syntax

Parameter	yes (n=)	no (n=)	borderline (n=)	not known (n=)
37	1	30	0	3
41	1	19	4	10
45	2	16	7	9

As can be noted, all children except one started to produce their first words remarkably late. Even the children with fewer anatomical problems in the pharyngeal area, and with less speech problems, only used very few words until they were over 2;6 years of age. The girl that did produce more than two words at

the age of 15 months actually had a 'non-classical', smaller deletion in the 22q11DS-region LCR C-E of about 1.5 Mb.

Most of the children begin to use a few words actively in the age range between 2;6 (years; months) to 3;6. Three children made sudden progress and started using more and more words after 4;0 years of age, although their expressive language level was still poor compared to typically developing children.

Often, parents mentioned that their child seemed to understand much more than would be expected based on language production. However, in many cases, the test results for receptive language were low as well, and actually lay rather close to the results for production. As can be seen in figure 6, TBQ ('taalbegripquotiënt', a measure for receptive language in the Reynell-test and the Schlichting-test, which is frequently used in the evaluation of Dutch-speaking children) was typically in the range of 70-90, and of the three children who scored relatively high on TBQ (>100) only one scored much lower on productive language (Schlichting WQ and ZQ range 70-80).

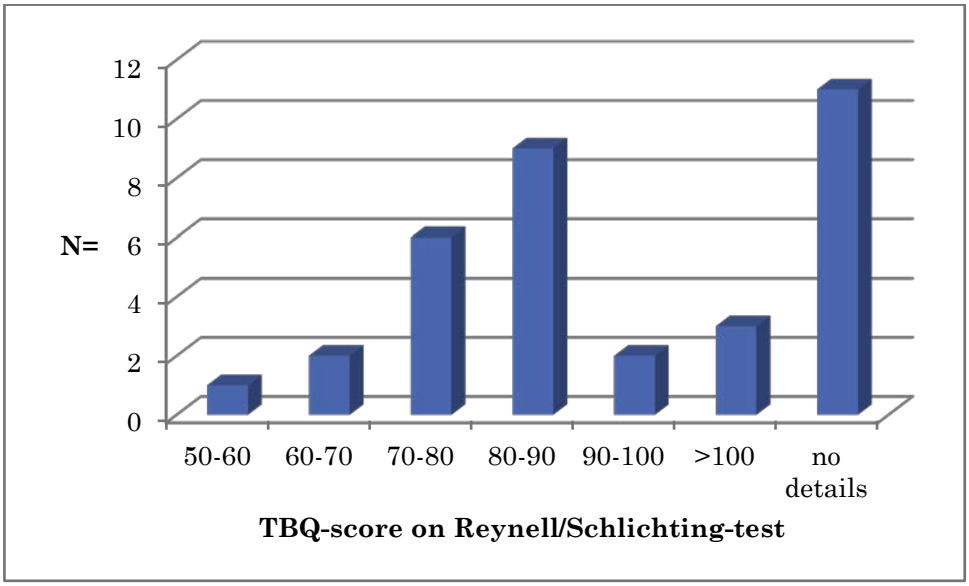

Figure 6 Overview available results for TBQ (Reynell/Schlichting)

Advanced syntax (sentences of more than 3 words)

Less information was available about subsequent development of expressive syntax. This is probably a result of the fact that many of the younger children did not yet speak in complete sentences. In the cases where information

was available, the children appeared to use one or two word-sentences for a much longer period than would be expected based on the Van Wiechen-criteria. In general, they used much shorter sentences than is expected at their age. Furthermore, the sentences were rather simple in structure. In some cases, speech language therapists and physicians mention in the files their observation that few functional words are used and that there is not much use of past tense, little use of inflection, few subordinate clauses, and not much use of inversion (inversion is frequently used in Dutch grammar, for example in sentences containing location or time adjuncts, in questions and in subordinate clauses.)

Although parents often mention that the receptive language abilities of their child are better than the expressive language abilities, this does not necessarily seems to be the case based on the information in the files. In many cases it appeared as if the children were 'guessing' the meaning of a sentence by picking up some words from the sentence and then trying to establish some sort of meaning from it. Also, when a difference in meaning was expressed by a grammatical construction, this was often a problem for children.

For example:

(1) Question adult: *"Wat moet je doen om water te laten koken*?"('What should you do to make water boil?')

Answer child: "*Eitjes*" ('Eggs')

(2) Question adult: *"Welk dier geeft melk?"* ('What animal gives milk?')

Answer child: "*Poes*" ('Cat')

(Compare: 'What animal do you give milk?')

In the examples above, it appears as if the child is not able to analyze the structure of the sentence, and therefore 'guesses' the meaning of the question based on the meaning of the nouns in the sentence, and using associations/knowledge of the world, possibly to compensate for a lack of knowledge about the grammatical structure of the sentence.

Also, it was mentioned in two cases that it was easier for the children to continue the answer to a question when the first part was already given than to construct a complete answer by themselves. For example:

(3) a. Question adult: "*Waar worden schoenen van gemaakt?*"

('What are shoes made of?')

Answer child: ?

b. Question adult: *"Schoenen worden gemaakt van..."*
('Shoes are made of...')

Answer child: "*leer*" ('leather')

(4) a. Question adult: *"Welke kleur heeft gras?"*

('What is the colour of grass?')

Answer child: ?

b. Question adult: *"Gras is...?"*

("Grass is ...?")

Answer child: "*groen*" ('green')

Again, it may be possible that the child does not understand the grammatical construction of the question (Wh-? + inversion), which makes it difficult for the child to understand the question.

Story telling

Not much information was found regarding the story telling abilities of the children. At one point it was mentioned that this is rather difficult to evaluate, because of the problems in semantics and syntax.

Pragmatics and non-verbal communication

Pragmatics appeared to be less of a problem. There were four children who showed problems in for example turn taking, assessing a listener's background knowledge and interpreting tone of voice and intonation. These children had been diagnosed with autism spectrum disorder (ASD). A connection between pragmatic problems and ASD seems plausible.

Most other children, by contrast, were generally very communicative, and some were frustrated if they could not make themselves be understood. They often used non-verbal modes of communication to make themselves clear. For instance, of 25 children reviewed (74%) it was mentioned that they used signs for communication, sometimes even self-invented signs. Three other children were said to use "non-verbal communication", but it does not become clear whether this means the use of signs, or other forms of non-verbal communication. Most children tried to clarify themselves further by pointing at things, by guiding people to things/places, by making sounds and by using intonation. Sign-supported Dutch was often used in speech language therapy.

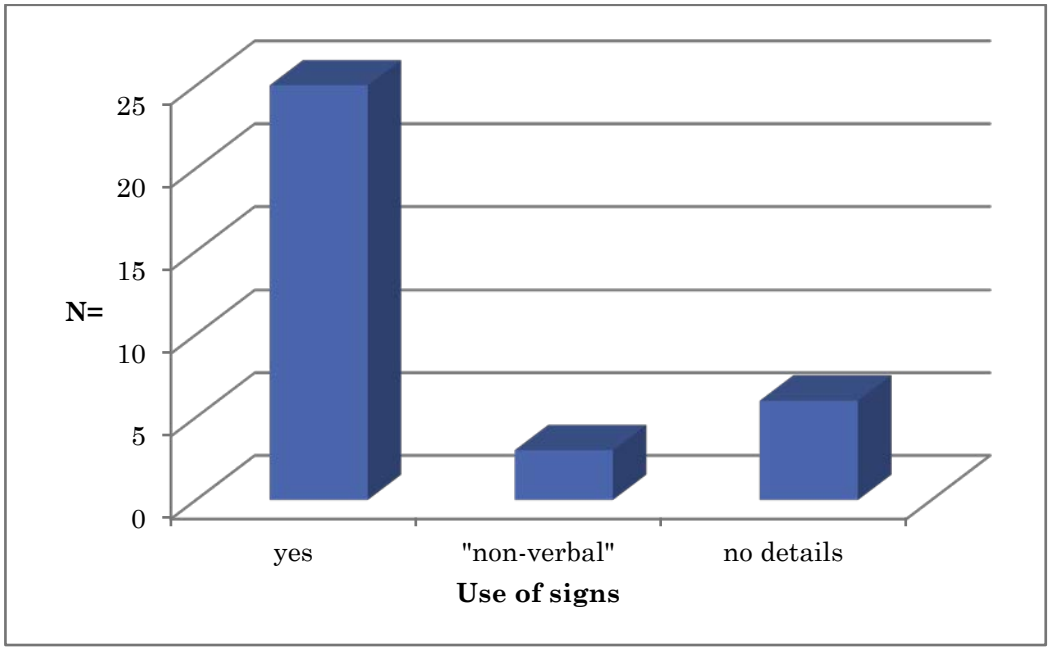

Figure 7 Overview use of signs as non-verbal communication

Discussion

Results

The main aim of this pilot study was to obtain a better understanding of the speech and language development in children with 22q11DS. The main research questions were: What are the characteristics of the speech and language development (phonology, semantics, syntax and pragmatics) in children with 22q11DS between the ages of 0 and 8-10, and in what way is this different than in typically developing children of that age group? Can anything be said about the clinical, psychological and genetic background of these children in relation to

language development? A qualitative, retrospective, multiple case survey was performed using the medical files of 34 children with 22q11DS between the ages of 0 and 8-10 years old and their language development.

The retrospective nature of this survey meant that the children were not all tested at the same age and with the same tests. However, the way in which the survey was performed made it possible to get a longitudinal perspective on the development of the child, and an interesting developmental pattern for speech and language in children with 22q11DS could be observed.

Many children showed (severe) hypernasal resonance, mostly caused by a palate that was too short, a malfunctioning velum and/or weakness in the muscles in the oropharyngeal area. Furthermore, many children had problems achieving enough intraoral pressure to adequately produce plosive and fricative sounds, and speech was often characterized by nasal emission and compensational strategies like backing, glottal reinforcement and cluster reduction. The majority of the children had a poor intelligibility.

The children with the most common, 'classic', deletion in the 22q11-region (a deletion of approximately 3 Mb between low copy repeats A and D) all showed a delay in the emergence of the first words. These results are consistent with what was found in earlier research by Golding-Kushner et al. (1985), Scherer et al. (1999) and Solot et al. (2000), as discussed earlier. There was only one child whose first words did not seem to be delayed. This child had a smaller deletion of approximately 1.5 Mb between low copy repeats C and E.

As was the case in the research done by Golding-Kushner et al. (1985), Solot et al. (2000) and Persson et al. (2006), most of the children used (sometimes much) shorter and less complex sentences than would be expected based on their chronological age. In some cases, the child seemed to be unable to analyze the grammatical construction of a sentence, and seemed to 'guess' the meaning based on the meaning of the nouns in the sentence. Again, the only child who did not seem to have any specific problems in using longer and more complex sentences was the girl with the smaller deletion of approximately 1.5 Mb between low copy repeats C and E.

Parents often mentioned that receptive language seemed to be better than expressive language. Results in earlier research were not in agreement about this. Glaser et al. (2002) even found an opposite pattern, as their results suggest that expressive language was better than receptive language. The test results of the children reviewed in this thesis do not show striking discrepancies between the measures for expressive language and for receptive language. In some cases, it appeared as if the child is not able to analyse the structure of the sentence, and therefore 'guesses' the meaning of the question based on the meaning of the nouns in the sentence, and using associations/knowledge of the world, possibly to compensate for a lack of knowledge about the grammatical structure of the sentence.

Children with 22q11DS utilize non-verbal communication to express themselves, and the majority of children used (sometimes 'self-invented') signs to help them communicate. Most of the children were in fact very eager to communicate. One may wonder if children do not use compensational strategies, for example by paying attention to the context in which the conversation takes place and the body language and intonation of the person who is speaking.

An important question concerns the reliability of the IQ-tests, as it can be very difficult to distinguish between language-related problems and intelligence-related problems a child might have during an IQ-test. How can one be sure that the child is not having any problems in understanding the question or assignment because of language problems? It could be argued that children with 22q11DS are in fact very intelligent, as in many cases, they use non-verbal aspects to communicate. They are therefore capable of estimating the knowledge the other person has, and finding ways to make things clear, something that would require quite some intelligence.

As was suggested by Solot et al. (2000), it seems as if the delayed speech and language development cannot be explained by cognitive factors alone. The IQ-scores of the children vary considerably between them (from mild mental retardation to average), but all children (but one) show problems in language development. This would suggest the presence of a specific speech and language impairment in children with 22q11DS.

Because of the retrospective nature of this survey, it was not possible to control for what tests were used and the age at which the tests were performed. This means that the same data were not available for all children. However, the way in which the survey was performed made it possible to get a longitudinal perspective on the development of children with 22q11DS.

Recommendations speech and language therapy for children with 22q11DS

After review of the selected medical files, the impression arises that the problems in language are often overshadowed by the speech problems. Often physicians do not differentiate between speech and language. It is easily assumed that the problems, especially regarding language, are a consequence of a cleft, of being hospitalized for a long time because of cardiac problems, of not hearing well (even if it is mentioned by the audiometrist that hearing is sufficient for speech and language development) or of the child being 'mentally retarded'. However, based on the results of this survey one can say that the speech and language difficulties are an integral part of the 22q11- deletion syndrome. Whether or not a child has a cleft, has been in the hospital for a long time, has an average IQ or has hearing problems, they all show more or less the same problems in speech and language. It is actually the most common shared feature of children with 22q11DS. Some of the children have clefts, some have cardiac problems, some have hearing problems, some have immune problems, but all the children with the 'classic' deletion in 22q11DS experience problems in the area of speech and language development.

It is therefore important that treating physicians and speech language pathologists become aware of the (sometimes severe) problems in speech and language development, and adapt treatment protocols accordingly. At this moment in time, the protocol for the treatment of speech problems in children with 22q11DS is often the same as for children with a cleft. This treatment is mainly directed at speech problems. The question is if this is actually the most appropriate treatment for children with 22q11DS. To a much lesser extent attention is paid during speech language therapy to problems in language

development, maybe because it becomes clear at an early stage how severe these problems are, or maybe because some therapists feel that the speech problems should be addressed first. In some cases, children do not receive any therapy at all at first (because of a 'wait-and-see policy').

When parents are asked what worries they have regarding the future of their child (after possible life threatening issues have been solved), they frequently answer that they worry most that their children will not be able to express themselves, and that this will influence their quality of life. Based on the results of this survey, one could argue that all parents of children born with 22q11DS should be advised at a very early stage by a speech language therapist, and receive information on what to expect as regards the speech and language development of their child and how to stimulate both speech and language development of their child. As the results of this study show that children with 22q11DS often use signs to make themselves clear, one could consider the use of signs to support verbal communication from a very early stage on, maybe even starting in the first year of life, both during therapy and at home.

Future Research Questions

This paper gives an overview of problems children with 22q11DS experience in their early speech language development, and also shows that a lot of questions remain unanswered.

This survey has made clear what problems in the area of language and speech exist in children with 22q11DS, but not what the origin of these problems is. If one wants to know how these children can best be treated with speech language therapy, it is necessary to try to find the exact cause of the problems. For example, is there a problem with working, declarative or procedural memory? Are there any problems in speech perception, is the child able to 'decode' the sound signal? Is the child not able to deduct grammatical rules? If more is known about the nature and origin of the language problems in children with 22q11DS, this could help to determine a possible treatment for their problems. More research into appropriate therapy for these children is necessary. For example, how effective is the use of sign-supported language in improving the language

development of the child? What can be gained from early intervention by a speech language therapist?

It is important that more specific linguistic tests are used in research into the nature of the language problems of children with 22q11DS, instead of more general psychometrical tests like IQ-tests. One could think of non-word repetition tasks or tests related to the acquisition of definite and indefinite markers, or verb inflection. In this way it would be possible to research more specific linguistic features than with for example a VIQ-test, in which it is difficult to distinguish linguistic features from non-linguistic features.

Furthermore, one could try to establish if there is a difference in brain structure or brain function that could explain the problems. If so, this could mean that the genes of which the child has only one copy play a role in the development of the structures or systems that allow speech language development. This in turn could also contribute to a better insight in the language faculty itself. In this context it was very interesting to see that the child who was reported to have a smaller deletion was the only child who did not seem to have problems in speech and language development. Although not for all children all genetic data were available, it would be very interesting to compare more children with a smaller deletion with children with the 'classic' deletion in future research.

Another interesting research issue would be to study the language abilities of children at a later age. How do these abilities develop over time? From earlier studies it is known that there is a decrease in IQ in children with 22q11DS over time. In the research of Golding-Kushner et al. (1985) the results suggested that older children with 22q11DS had more severe problems if compared with their typically developing peers than younger children. Is there a direct correlation between age and language development in children with 22q11DS?

It is clear that there are a lot of interesting research questions are still open to be answered.

Conclusion and recommendations

With the present study, I investigated if a pattern can be observed in the language development of children with 22q11DS between the ages of 0 and 8-10

years. If this kind of pattern could be observed, this could help in predicting outcomes and in deciding if early intervention is necessary. It could also suggest relevant future research questions.

Almost all (all but one) children reviewed showed (severe) impairments in speech language development. For one of the children, the delay in speech language development, combined with some facial features typical for 22q11DS, was in fact the reason to consider genetic testing for 22q11DS. The only child who did have clear signs of a developmental problem in speech and language had a non-classic, smaller deletion of 1.5 Mb in the 22q11DS-region.

The above is a general overview of the findings from the reviewed files. Although the children were tested at different ages and using different test methods, it is possible to see striking shared aspects of language developmental problems in these children. For the children it is often frustrating to not be able to express themselves adequately and parents often mention the problems in speech language development as a major concern they have regarding the future of their child.

Although it is often assumed that the delay in language development is caused by VPI or a cleft, or mental retardation, the results of this study suggest otherwise. All children, whether they have a cleft or not, if they suffer from VPI or not and whether they score low or average on IQ-tests, show a delay in early language development. Therefore, the problems in language development seem to be

More specific research regarding language development in children with 22q11DS is necessary. If more insight in the early language development of these children is gained, this would make early diagnosis, appropriate intervention and maybe a prognosis of language outcomes at a later stage in life possible. Early intervention could possibly affect language outcomes later in life in a positive way. From a very early stage, parents of children with 22q11DS should be guided in relation to what they can expect of the speech and language development of their child and how they can best stimulate the development of both speech and language in their child.

Last but not least, understanding more about the nature and origin of the language problems in children with 22q11DS could help understand more about the human language faculty in general.

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Appendix 1 Overview first words and early syntax

Child	M/F	2 wrds < 15 mnths	Combination of 2 wrds < 2 yrs	Combination of 3 wrds < 3 yrs
1	F	no	no	not known
2	F	no	no	no
3	M	no	no	no
4	M	not known	not known	not known
5	F	no	no	no
6	M	no	no	no
7	M	no	not known/borderline?	not known, probably no
8	M	no	no	no
9	M	no	no	no
10	F	no	not known	no
11	F	no	not known	not known/borderline?
12	F	no	not known	not known
13	M	no	borderline?	yes, borderline
14	M	no	not known	borderline?
15	F	not known	not known	not known/borderline?
16	M	no	no	no
17	M	no	no	not known, probably no
18	F	no	borderline?	yes,borderline
19	F	no	no	no
20	F	no	not known	no
21	F	no	no	no
22	F	no	no	no
23	M	no	no	no
24	F	no	no	yes
25	M	no	not known	no
26	F	no	not known	not known
27	F	no	no	not known, probably no
28	M	no	no	not known/borderline?
29	F	not known	not known, probably no	not known, probably no
30	F	no	no	yes,borderline
31	F	yes	yes	yes
32	M	no	no	no
33	M	no	borderline?	yes,borderline
34	M	no	no	no

Appendix 2 Results per child

Patient	1	2	3	4	5	6	7	8	9
Age at study	6;8	9;3	7;10	9;3	7;3	7;8	6;9	5;8	4;5
Age at diagnosis	<1;0	0;9	<1;0	no details available	3;2	3;5	0;1	0;1	0;2
M/F	F	F	M	M	F	M	M	M	M
Hypernasal	yes	difficult to evaluate	yes	yes	yes	yes	yes	difficult to evaluate	yes
Understandibility	moderate	good	poor	poor	poor	poor	poor	poor	poor
Babbling as baby	no	no details available	no	no details available	no	no details available	yes (0;10)	yes	no details available
Fonology	3;1: cluster reduction	6;11: cluster reduction	6;0: substitution of consonants, cluster reduction	4;11: 'incorrect articulation of some sounds'	3;3: uses predominantly vowels; 4;5: cluster reduction; 6;6: glottal reinforcement	4;5: nasal emission consonants	3;3: cluster reduction; 4;0: nasal emission on fricatives, backing and glottal reinforcement on plosives; insufficient intraoral pressure plosives	2;8: uses predominantly vowels, sufficient intraoral pressure plosives; 3;4: is able to produce all sounds separately, but not yet in combination	1;8: uses only few sounds; 1;11: uses predominantly vowels; 3;2: insufficient intraoral pressure plosives, nasal emission, glottal stops and glottal reinforcement
Onset of talking	2;2: uses only a few words,understanding seems ok	4;9: uses only few words, and sounds	3;0: uses only few words	no details available	3;3: only uses 3 words, understanding seems ok	2;5: uses only '*ja* '(= yes), '*nee* '(= no) and '*daar* ' (= there); 2;11: knows about 30 spoken words, and some signs	2;0: NCDI both active and passive vocabulary < 1, 2;6: uses '*kij(k)*' (= look), '*papa* ' en '*mama* '	3;4: uses a few words of a simple structure	1;8: uses 'a few' words; seems to understand more;
Sentence length and structure	2;2: does not yet make combinations of words;	6;11: uses short sentences (2 to 3 words); little use of auxiliary verbs and no conjugation for past tense	no details available	5;10: uses simple phrase structure, problems in word order (no inversion), little conjugation of verbs, problems with subordinate clauses	5;9: frequent use of 1-2 word sentences	3;1: makes sentences of 1-2 signs (no data available about spoken language)	4;0: uses 3-word sentences, but gets more difficult to understand; 5;5: uses short sentences	3;10: uses 1-2 word sentences, sometimes 3-4 word sentences, but these are not formed well, verb use is often incorrect, often seem to be standard phrases	3;5: uses predominantly 1 word utterances; no past tense, understands a few prepositions
Story telling	4;11: very poor	no details available	no details available	no details available	difficult to evaluate because of poor understandibility	no details available	5;5: poor	no details available	no details available
Pragmatics	no details available	6;11: does not understand significance of tone of voice, turn taking, word jokes.	no details available	no details available	does use intonation, but not always adequately; does not really understand turn taking, uses a lot of standard questions	no details available	2;6: normal prosody	no details available	no details available

Patient	10	11	12	13	14	15	16	17	18
Age at study	8;4	5;10	9;0	6;4	4;1	8;0	8;4	5;5	6;7
Age at diagnosis	approx. 2;0	0;2	2;5	approx. 2;0	0;2	2;8	1;6	0;1	0;4
M/F	F	F	F	M	M	F	M	M	F
Hypernasal	no	yes	moderate	difficult to evaluate	moderate	hyponasal	no	yes	moderate
Understandibility	moderate	poor	poor	poor	poor	poor	good	poor	moderate
Babbling as baby	no details available	yes	no details available	no	yes	no details	no details	2;0: "started babbling more frequently lately"	yes
Fonology	3;2: sufficient intraoral pressure plosives, cluster reduction, "no phonological problems associated with VPI"	1;7: palate lifts only slightly; 2;4: 'very limited sound collection'; 3;2: uses predominantly vowels; 3;10: cluster reduction; 5;6: 'almost all sounds acquired', slight nasal emission and turbulence on plosives	3;10: glottal stops; 4;9: glottal reinforcement	2;3: backing; 4;1: moderate intraoral pressure, sometimes nasal emission on plosives, cluster reduction	2;9: intraoral pressure not always sufficient;	3;6: speaks with a lisp; cluster reduction; 5;2: sometimes still cluster reduction	5;5: omission of consonants (especially at word ending), backing, assimilation, clusterreduction	2;0: insufficient distinction between nasal, plosive, fricative and liquid sounds, glottal reinforcement; 3;11: nasal emission plosives/fricatives, insufficient intraoral pressure	3;9 and 4;9: backing and nasal emission on fricatives and plosives, intraoral pressure seems sufficient
Onset of talking	2;7: Has just started to use first words; 3;7: seems to understand more than expected based on production, uses her 'own' signs	1;7: only uses '*mama* ', imitates signs and animal sounds; 3;2: more attempts at speaking	2;8: hardly speaks, only answers to question: 'What is that?'	1;5: uses only '*mama* '; 2;3: only uses six words, mainly '*papa* ', '*mama* ' and names siblings	1;6: uses only '*mama* ' and '*amen* '	no details	2;8: predominantly sounds, not real words 4;6: little verbal production (uses approx. 15 words actively); 5;5: little use of verbal communciation; 6;5: small steps forward, communicates predominantly verbally	2;0 jr: can produce 'mama', understanding not clear; 2;3 jr: few words /aa/ = '*auto'* (=car) *'hallo', 'doei' (= bye), 'mama'* and *'oma' (=* gran*);* 2;9 jr: uses 'mama' for almost everything; 3;11 jr: seems to understand what is being said, but hardly speaks 4;11 jr: "wants to say more, but does not seem to know how'	1;11: uses ~5 nouns 2;1: starts to use more words: exclamations, nouns and adverbs, no verbs
Sentence length and structure	4;6: 'picks 1 or 2 words from sentence and tries to deduce meaning from this'; 4;8: uses 2-3 word sentences supported by signs; 5;8: short sentences, few functional words, few complex structures, verbs not always used properly, vervoeging verbs not always right, few subordinate clauses	3;2: uses sentences of more than 1 word, but not comprehensible, uses signs; 4;4: uses 3-4 word sentences	no details available	2;3: uses 1 words sentences and some 2 word sentences; 3;3: speaks in short sentences with simple structure	3;4: uses 1-4 word sentences	3;6: 1-3 word sentences; 7:7: incorrect used of articles	6;5: 'starts making sentences'; 8;1: 'makes longer sentences'	3;11: 2-3 word sentences; 4;11: "starts to make longer sentences"	1;11: no 2-words sentences; 2;1: predominantly 1 word-utterances, very few 2-word utterances; 2;6: 1-3 word sentences; 3;9: 'understanding in accordance with age; word- and sentence development below average'
Story telling	Poor	no details available	no details available	no details available	no details available	no details	no details	no details	no details
Pragmatics	4;6: does not understand word jokes or double meanings of a word; does not take into account background knowledge of listener	1;6: senstive to intonation, takes initiative to communicate, 1;7: cries, uses facial expressions and intonation to communicate.	no details available	no details available	no details available	no details	no details	no details	no details

Patient	19	20	21	22	23	24	25	26	27
Age at study	8;1	6;2	6;11	8;0	8;0	4;7	6;3	8;4	6;1
Age at diagnosis	2;10	0;0	0;1	0;0	0;0	0;1	0;0	<1;2?	0;3
M/F	F	F	F	F	M	F	M	F	F
Hypernasal	yes	yes	slightly	yes	no	slightly	yes	yes	yes
Understandibility	poor	poor	moderate	poor	poor	poor	no details	poor	poor
Babbling as baby	no details	yes	yes	no	late (>1;5)	yes	yes	yes	yes
Fonology	3;1: uses predominantly vowels; no differentiation between vowels; 3;7: insufficient intraoral pressure	3;6: nasal emissions, turbulence, glottal reinforcement, insufficient intraoral pressure	4;1: cluster reduction, intraoral pressure plosives sufficient	4;10: glottal reinforcement, cluster reduction; 5;3: backing and assimilation; sufficient intraoral pressure plosives, 5;10: sometimes nasal emissions/turbulence	1;5: babbling according to mother 'dada, 'oh', 'tatata', (for all animals) 'eheh' while pointing at something; 5;5: cluster reduction, sufficient intraoral pressure plosives	3;0: sometimes nasal turbulence in plosives	3;7: moderate intraoral pressure plosives/fricatives	2;5: uses predominantly vowels and some consonants; glottal reinforcement; 4;0: nasal emission; 5;8: backing, glottal reinforcements, nasal emission	3;3: insufficient intraoral pressure; 3;11: glottal reinforcement
Onset of talking	3;1: speaks few words that can be understood within context: '*ja* ', *'nee', 'appel' , 'banaan', 'klaar* ' (= finished)	1;7: uses few words ('*mama* ' and sometimes '*papa* '), 'understanding seems ok';	2;1: 'uses a few words'	2;9: understanding reasonable according to parents; 3;0: uses 2 words with meaning'; 4;0: '*ja* ', '*mama* ', '*papa* ', '*hajo* ' (= 'hallo'), '*oef* ' (= 'poes'; cat);	1;9: says '*dat* ' (= that), '*tuig* ' (from 'vliegtuig' = airplane) for anything that flies,no '*papa* ' or '*mama* '; 2;9: active vocabulary 15 words (+ 10 signs); 4;3: 'understanding better than production', 4;5: 1-word utterances with supporting signs	1;2: seemed to use '*mama* ' in a meaningful way for the first time; 3;3: 'understands about 100 words'; 3;11: 'vocabulary improved'	1;4: 'does not yet use words'; 2;1: uses '*mama* ', but not specifically for mother; uses '*nee* ', but not always adequately; at one occasion he has reacted adequately to his name;	1;2: '*mama* ' (not clear if directed specifically at mother), and babbling '*nene* ', '*jaja* '; 8;0: retrospective "first words and sentences on time" (no details available)	1;11: babbling, but no words yet; 2;8: moderate receptive language according to parents; 3;1: uses only '*mama*' (for both mum and dad); 3;11: 'doubts about vocabulary'
Sentence length and structure	3;1: 1-word utterances and very few 2-word sentences; question without visual support has to be repeated several times before she understands; 3;7: 1-3 word sentences; 5;8: problems repeating (grammaticaly complex) sentences	no details	3;2: starts to combine words in 2 word-sentences; 4;1: produces 3-5 word sentences	4;0: predominantly 1-word utterances, sometimes 2-word sentence; 5;3: 2-3 word sentences; 5;9: predominantly 2-3 word sentences;	4;3: predominantly 1-word utterances with supporting signs, sometimes 2-word sentence ; 5;5: 'short sentences'; 6;10: 'speaks in short sentences'	3;0: uses 2-3 word sentences 3;11: uses sentences 4-7 words	3;7: uses 1-word utterances; 3;11: predominantly 2-word sentences; 4;0: 3-4 word sentences; 5;0: 4-word sentences	5;3: less problems with finishing someone else's sentence than with constructing a new sentence.	2;8: understands simple requests, during examination, 1x 2 woordszin '*mama ook* ' (= mum too) ; 3;11: 3-word sentences; understands simple requests and some more complex requests; prepositions are not always understood correctly; 5;10: 'seems to be behind with regards to sentence structure'
Story telling	no details	no details	no details	no details	no details	no details	no details	8;0: often starts in middle of story, does not take in account the knowledge of the listener sufficiently	no details
Pragmatics	no details	5;7: talkative, but does not answer to the question posed	no details	1;9: turntaking still in development	2;7: eye contact, turntaking and imitation insufficient, easily distracted; 5;5: speaks outside here and now	no details	4;3: eye contact and turntaking ok	1;2: turntaking and eye contact ok; 5;3: associative in answering, does not answer the original question; 8;0: very associative,	2;8: does not imitate sufficiently, sufficient contact with parents, does not communicate outside 'here and now' ; 3;3: seems to be able to follow conversation; 3;11: turn-taking, eyecontact and listening behaviour insufficient

Patient	28	29	30	31	32	33	34
Age at study	7;5	9;11	9;1	6;1	8;2	7;11	9;3
Age at diagnosis	0;1	<0;10	2;4	0;1	~2;8	~0;10	no details available
M/F	M	F	F	F	M	M	M
Hypernasal	no	yes	no	no	yes	moderate	no
Understandibility	moderate	poor	good	good	moderate	moderate	no details available
Babbling as baby	yes	no details	no details	yes	late (~2;10)	yes	no details available
Fonology	3;4: 'problematic phonological development', insufficient intraoral pressure, glottal reinforcement; 5;3: 'speech ok for someone with 22q11DS'	3;2: cluster reduction, assimilation; 4;2: cluster reduction, nasal emission, 'phonological development not completed'	2;9: 'phonological development seems to fit level of language production'; 3;11: phonological development conform age	2;5: not all phonemes have been acquired yet	2;9: intraoral pressure seems adequate; 3;4: backing, nasal emission	5;0: intraoral pressure varies; nasal emission fricatives en plosives	2;2: not much variation in sounds, mouth area seems hypotone
Onset of talking	2;0: '*mama* ' and '*papa* '; 2;5: uses few words	no details available	1;1: 'first words'; 1;9: uses only a few words, seems to understand more;	1;10: "speech and language development seems to be adequate"	3;0: "just started to speak first words", does seem to understand language	1;1: uses word '*auto* '(=car); 1;10: 'uses a few words'	2;0: no words yet; 2;2:'*mama* ', '*papa* ' and some exclamations, receptive language seems ok
Sentence length and structure	2;5: no 2-words sentences, understanding seems ok; 3;4: 1-3 word sentences; 5;6: 'language understanding seems average/below average, vocabulary below average'	3;3: 'speaks in simple, multiple word sentences'; 7;4: 'insufficient semantical and grammatical development'	1;10: '1-word utterances, no 2 word sentences'; 2;4: 1-word utterances, sometimes a 2-word sentence; 2;9: uses 1-2 word sentences; 3;6: 4-5 word sentences; 3;11: level of language development not clear (difficult to test)	1;10: uses 1-word utterances, some 2-word sentences; 2;5: uses words during play, short sentences; 2;9: 2-4 word sentences; 3;5: 2-5 word sentences; 3;10: finds it at occasion difficult to answer open questions, but can finish sentences: "Grass is …" instead of "What is the colour of grass?"	3;4: uses 1-word utterances, sometimes 2-word sentence; 4;9: uses sentences of a simple structure	2;6: parents feel his speech and language develoment is delayed compared with his peers, 1-3 word sentences; 2;11: 1-4 word sentences; 5;2: "level of speech language development not constant" ; 6;2: uses long sentences, both of a simple and a complex structure	7;10: uses short sentences or 1-word utterances, seems to have problems in structure of sentences, associative answers
Story telling	no details	8;9: can speak outside 'here and now', sometimes difficulty in making connections, causal relationships, shy in group setting	no details	no details	no details	no details	no details
Pragmatics	1;2: 'makes good contact'; 4;7: sufficient eye contact	3;2: normal eye contact, likes to communicate; 7;4: associative in answers	2;4: normal eye contact; 2;9: normal verbal imitation, does not take much initiative to speak	2;5: normal eye contact; 2;9: speaks in 'here and now', asks questions, uses spoken language as means of communication	2;10: does not ask to repeat if he does not understand something; 3;4: more inititiave to speak, more communicative	5;2: associative in answers	2;2: normal eye contact, turn-taking and imitation

Patient	1	2	3	4	5	6	7	8	9
Non-verbal communication	2;2: pointing, guiding people, using signs, facial expressions, very communicative	Focuses on signs and imitates signs	3;0: uses signs to communicate	no details available	3;9: uses signs to communicate	5;3: uses spoken language in relaxed situations, otherwise prefers to use signs	2;6: uses 'uh' in combination with signs to communicate; 4;0: cannot express himself sufficiently verbally, uses signs as support	3;10: uses signs and facial expression to support verbal communication	2;0: uses signs to communicate 4;4: communicates predominantly nonverbally at school, but very eager to tell things
Cleft/VPI	bifid uvula	no	malfunctioning velum (operation 2011)	cleft palatum molle (operation 2013)	Bifid uvula, no cleft	Submucous cleft, operation for VPI in 2010	Bifid uvula, insufficient movement left side larynx, compensated by right side (operations in 2010, 2012 and 2014)	Bifid uvula, suspected submucous cleft	no cleft, operation for VPI
Hearing problems	no	Some doubts about hearing; test results not clear	Conductive hearing loss 25-30 dB both sides	chronic otitis media	Slight conductive hearing loss, test results differ	Conductive hearing loss both ears -40dB/-60dB, wears hearing aid	no	no	Frequent otitis media
test-scores	2;2:Reynell TBQ93, N-CDIS: passive vocabulary p 30-35, active vocabulary p <1; 2;11: TBQ:102; 3;8: WBQ: 96, TBQ: 101, WQ: 100, auditory memory: 82; 4;11: TBQ: 99, WQ: 83; auditory memory: 116,	3;8: SON-IQP 72, SON-IQ R 52	IQ 75 (not clear what test was used)	4;9: Schlichting WQ: 92, ZQ: 97	2;11: Reynell TBQ 87; 3;8: SON-IQ 78 (RS 76, PS 85); 5;3 jr: SON-IQ 80 (PS 70, RS 96)	2;5: BSID-III MS 85 (corrected for prematurity); 2;4: TBQ 82 (corrected); 3;1: Reynell TBQ 78, Schlichting ZQ 83 WQ72; 3,11: Reynell TBQ 78; Schlichting WQ 80; 4;0: Schlichting ZQ 80; 4;8: Reynell TBQ 73, Schlichting WQ 80	3;8 jr: Schlichting WQ64 , ZQ74 auditory memory 84, 3;10: SONIQ 92, SONRS 85, SONPS 100; 6;4: Schlichting WQ 74, ZQ 74, TBQ 78, Peabody PPVT-III-NL 91	2;0: Reynell TBQ 72; 3;0: Reynell TBQ 77; 3;10: SONIQ 79; SONRS 83; SONPS 79, Peabody 63.	2;0: BSID-II-NL: cognitive subtest 100, 3;5: Wechsler WPPSI-III-NL: VIQ:100, PIQ: 80, TIQ:89, language index 94.; 3;6: Schlichting TBQ 98, word development 91, sentence development 81, auditory memory 101.
Genetic profile	no details available	mother also has 22q11DS (diagnosed at 38 yrs), no further details available	de novo, no further details available	no details available	3;2: deletion of ~ 2.8 Mb in 22q11.21 (A_18_P13956448-> A_16_P41484416; 181 oligo's; multiple genes), unequal recombination between low copy repeats A and D, de novo	no details available	classic' unequal recombination between low copy repeats A and D of ~ 3 Mb, de novo	no details available	classic' unequal recombination between low copy repeats A and D of ~ 3 Mb, de novo
Cardiac problems	Tetralogy of Fallot	Tetralogy of Fallot	Tetralogy of Fallot	no details available	no	no	coarctation of the aorta	Tetralogy of Fallot	Operated right after birth: interrupted aorta, VSD and restrictive ductus
Autism	no	yes (4;11: diagnosed classical autism)	no	no	yes	no	no	no	no
Other	Slow speech language development in combination with facial features was indication for genetic testing; feeding problems first months	5;2: referral to child neurologist because of seizures, results of evaluation not clear			Is very willing to communicate and gets frustrated if not understood	Born at 26+5 weeks. Long term feeding problems, many airway infections	Dysphagia in first months	Dysmature, dysphagia in first months	Hirschsprung Disease, nasal resurgitation in first months, many airway infections

Patient	10	11	12	13	14	15	16	17	18
Non-verbal communication	4;6: uses signs as support for spoken language	3;10: uses signs as support for spoken language	2;8: uses prosody, facial expression ands signs as support	2;3: communicates mainly nonverbally	2;1: uses facial expression, eye contact; 2;9: mostly non-verbal communication (pointing)	7;7: makes eye contact	2;8: uses signs; 4;6: communicates predominantly non-verbally (signs, pointing and use of pictures), takes initiative to communicate non-verbally, 5;5: little verbal communication, predominantly signs to communicate	2;0 jr: uses mimic, sounds, many non-verbal utterances; 2;2 jr: communicates with signs (approx. 20 signs); is communicative and makes ey-contact 3;9 jr: communicative in use of signs, at day care sign-supported Dutch is used	2;11: uses signs to support communication
Cleft/VPI	no cleft, palate of sufficient length	no cleft, little lifting palate; 3;11: operation for VPI	no cleft, 6;0: operation for VPI	no cleft, functioning velopharyngeal area reasonably well	0;2: bifid uvula, no cleft; 0;7: little lifting of velum; 0;9: veloplastic surgery; 1;6: palate of sufficient length	Bifid uvula; 4;1: anatomically normal palate 5;2: VPI not clear, does not like to talk; 7;3: palate does not lift wel, no operation	5;5: normal palate, normal lifting; 6;5: there seems to be no VPI, hypotone mouth region	0;3: no cleft; asymmetric crying face; 1;2: palate slightly too short, does not move sufficiently; 2;9: lateral contractions, little mimic, little facial motor; 3;11: hypotone	0;2: bifid uvula, no cleft, 'musculature of palate seems different'; 1;11: palate does not lift sufficiently; 3;9: palate of enough length; 5;10: Honig-procedure
Hearing problems	3;7: tubes because of otitis media	Doubts about hearing, results testing ok; 4;10: tubes because of otitis media	Audiological tests normal, frequent otitis media	1;11: hearing tested after meningitis, test results normal; frequent otitis media	0;2: neonatal screening ok; 1;4: raised hearing threshold in a subjective test; normal hearing threshold right ear in high frequencies; left ear mildly raised hearing threshold of 15dB auditory neural processing brain stem borderline normal.	4;4: ADS otorroe, -/-30dB conductive hearing loss; 5;2: AS normal hearing, AD -/- 35-40 dB because of infection; 7;3: AD -/- 60dB, AS normal	no	3;11 jr: slight hearing loss of -/- 15 dB both sides; frequent otitis 4;11 jr: tubes because of hearing problems	no hearing problems, 1;0 and 2;11: tubes placed because of OME
test-scores	2;4: BSID OI 82; 3;5: SON-IQ 82, SONP 76, SONR 91; 3;7: Reynell TBQ 93; Schlichting WQ 95; (4;1: Reynell TBQ 85; 4;9: WIPSSI-III-NL: TIQ 77, VIQ 87, PIQ 83; processing speed 67, language index 75; 5;4: Schlichting TBQ 63, WQ 82.	1;7: BSID-II-NL: mental score 85, non verbal 89; 3;2 jr: TBQ 108; 3;7: WPPSI-III-NL VIQ 91, PIQ 97, Total IQ 92; 4;4 jr: Reynell TBQ 114, Schlichting WQ105, ZQ82;	2;8: NCDI 2A parent questionnaire: passive vocabulary p10-15, active vocabulary p3-5 ; SONIQ 81, SONPS 81, SONRS 81; 3;7: Reynell TBQ 84, Schlichting ZQ 93, WQ 87; 5;6: Reynell TBQ 89; 8;9: WISC-III, TIQ 78, VIQ 92, PIQ 67.	2;11: Reynell TBQ 80, 3;0: Schlichting ZQ 79, WQ 82;	2;7: Schlichting TBQ64; 3;4: PIQ 92 3;6: Reynell TBQ81, Schlichting ZQ88, Schlichting WQ83.	3;6:BSID-II-NL: developmental index 64 4;2: Schlichting TBQ83; 5;0: Schlichting TBQ 87, ZQ 98 ; 7;7: WISC-III-NL: TIQ 71, VIQ 72, PIQ 76	2;9: TBQ71, with supporting signs TBQ87; 5;4: TBQ 55 6;5:TBQ 63	2;11: SON-R: 84, SON-RS: 97, SON-PS: 74; 3;3: PPVT-III-NL: WBQ 63 (SD -2,5), Schlichting TBQ 61, WQ 55, ZQ 64; 4;0: SON-IQ: 67, SON-RS 81, SON-PS: 60, Schlichting WQ 64, ZQ66	1;11: NCDI-IIA: passive vocabulary p40-45, active vocabulary p 1-3. 3;6: Schlichting TBQ 101, WQ 70, ZQ 79; 6;6: WQ 76, ZQ 77, auditory memory 95
Genetic profile	no details available	classic' unequal recombination between low copy repeats A and D of ~ 3 Mb, de novo	no details available	no details available	classic' unequal recombination between low copy repeats A and D of ~ 3 Mb, de novo	no details	no details	deletion of ~ 2,8 Mb in 22q11.21 (17.04-19.84 Mb; 138 oligo's; multiple genes). ; de novo	classic' unequal recombination between low copy repeats A and D of ~ 3 Mb, de novo
Cardiac problems	VSD	peripheral pulmonary stenosis	no	right descending aorta,	mild pulmonary branch stenosis	double aortic arch, arteria lusoria	no	no	VSD
Autism	yes (with comorbide ADHD)	no	no	no	no	no	no	no	no
Other	many respiratory tract infection	Dysphagia in first year, neurological problems (sometimes sleeps with eyes open)	Nasal resurgitation in first year. Good short term memory, seems if she understands, but she just repeats	Nasal resurgitation in first months	Feeding problems first months, many respiratory tract infections	As a baby swallowing problems and nasal resurgitation	premature, many respiratory infections	0;0: dysmature, admission to NICU because of swallowing/feeding problems; 0;4: nasal resurgitation; 0;10: frequent respiratory tract infections	first years feeding problems, nasal resurgitation; 5;2: diabetes mellitus; 6;4: regular elementary school, maths according to age, language poor

Patient	19	20	21	22	23	24	25	26	27
Non-verbal communication	3;1: communicates by making sounds and pointing; 3;7: learns signs to support communication, uses intonation to make herself be understood	1;7 and 5;7: uses signs to support communication	0;8: communicative and alert, normal face-directed behaviour and auditory attention; 3;2: uses signs to convey a message; 4;1 and 5;2: uses signs to support communication	1;9: points at objects; 2;9: uses signs at home and at daycare actively; 3;6: use of supporting signs, points at objects, leads parents somewhere to make something clear; 4;10: uses signs to clarify spoken message; 5;3: supporting signs; 5;9: uses sign supported Dutch; 7;4: likes to communicate, uses spoken language as means of communication, but still uses supporting signs sometimes	0;9: eye contact ok; 2;9: uses supporting signs, imitates signs; 4;0: uses signs to communicate; 4;3: spoken language supported by signs, mimics and intonation; 5;5: uses supporting signs	no details	2;1: uses natural signs to support communication; uses pictures to communicate; 2;10: parents have started using sign language, he has learned to use them quickly, is able to communicate non-verbally quite well	no details	2;2: started using supporting signs; starts to imitate signs; 2;8: predominantly non-verbal communication; non-verbaal'; 3;3: uses signs, body language and facial expression to support communication;
Cleft/VPI	3;1: hypotone oral area, velum seems normal, no cleft; 5;0: surgery to improve speech	bifid uvula, no cleft, 4;3: no complete closure of palate; 4;9: Honig- procedure	no, palate does not seem to lift	no cleft, velum does not lift sufficiently	2;7: laryngeal cleft grade 1/2 confirmed; 2;11: laser surgery for laryngeal cleft	0;2; normal palate, no signs of submucous cleft; 3;0: VPI unclear	Yes, both palate and lip 0;6: surgery on palate, 0;10: surgery lip	submucous cleft (1;9: surgery); bifid uvula	no cleft, velum seems to not close off the oral cavity
Hearing problems	3;1: both sides ~-/- 40/50 dB; 3;2: OAE left normal emission, right cannot be determined; 3;6: BERA under anesthesia both sides -/- 20-25 dB; 4;2 AD -/- 5-dB, AS -/- 35 dB	no hearing problems, 2;2: tubes	no	2;5: hearing aid AD -/- 50dB high frequencies, 'probably cochlear problem', AS -/- 40dB, 4;10: AD+AS -/- 50dB, right perceptive, left mixed; 7;3: treshold with hearing aid 40dB, without AD/AS -/- 60-65	0;2r: BERA-test: slight hearing loss both sides -/- 25dB in high frequency, probably conductive ; 3;3: subnormal hearing both sides -/- 15dB, sufficient for speech language development 5;5: no doubts about hearing	0;2: post partum BERA ok; 4;0: tubes, seemed to hear better after this, AS treshold 10dB, AD treshold 20dB, sufficient for speech language development, 4;5: seems to be sensitive for (loud) sounds	0;10: at times his hearing is bad because of otitis media	1;4: persisting otitis with effusion; 1;9: normal audiogram; 8;0: very sensitive to sounds, quick to cover ears with hands	2;11: BERA under anesthesia, both sides hearing loss -/- 35 dB, probably mixed; hearing insufficient for normal speech perception; 3;1: trial with hearing aids, seems succesful
test-scores	3;6: Reynell TBQ 74, Schlichting ZQ 64, WQ 69; 5;8: WBQ 82, WQ 74; 5;11: SON-IQ 101, SON PS 97, SON RS 110; 6;1: Schlichting ZQ 70, Peabody III-R passive vocabulary WBQ 82, active vocabulary WBQ 93	4;4: SONR 2,5-7: TIQ 68, PS 65, RS 78; 5;7: WPPSI-III-NL 2,5-8 jr: TIQ 72, VIQ 91, PIQ 67, processing speed 55, visual-motor integration 79, visual perception 66, motor co-ordination 73	3;3: Schlichting TBQ 72; 3;8: TBQ 56, WQ73, ZQ 70; 4;0: TBQ 67, WQ 63; 4;1: ZQ 69; 5;3: Schlichting TBQ percentile score 3, Peabody PVT: percentile 19	1;9: NCDI-2A: parents questionnaire, language age < 16 months, both expressive and receptive; 5;3: Schlichting receptive language 'level of child of 2;4'; 7;3: Wechsler non-verbal scale of ability: total score 55	2;7: Reynell TBQ 72; 5;11: WPPSI-III: TIQ: 66, OS 64	4;0: TBQ: 84, WQ: 86, ZQ 83, AGQ 94	3;11: SON-IQ 68 (LE 2;8 jr), TBQ 73; 4;0: WQ 90, TBQ 82, ZQ 78; 5;0: TBQ 82, ZQ 78	1;5: BSID-II-NL: OIMS 99, OIMR 84, OI NV 98; 3;0: BSID-II-NL OIMS 108, OIMR 79 5;3: WPPSI-III-NL: VIQ93, PIQ87, TIQ 87; 8;0: WISC-II-NL TIQ 76, VIQ76, PIQ 80	2;2: Reynell TBQ 72; 3;11: Reynell TBQ 79, Schlichting ZQ 88, WQ 80, PPVT passive vocabulary 88
Genetic profile	no details	classic' unequal recombination between low copy repeats A and D of ~ 3 Mb	'classic' unequal recombination between low copy repeats A and D of ~ 3 Mb	unequal recombination between low copy repeats A and E of ~ 4 Mb	no details available	unequal recombination between low copy repeats A and D of ~ 2.5 Mb	classic' unequal recombination between low copy repeats A and D of ~ 3 Mb	no details available	no details available
Cardiac problems	no	0;0: operation interrupted aortic arch type B, VSD, ASD; complicated by paralysis left larynx	several cardiac problems, pulmonary atresia with large VSD, overriding aorta, major arterial pulmonary collateral arteries (MAPCA's)	0;0: NICU because of cardiac evaluation: Truncus arteriosus, VSD and ASD; 0;2: heart surgery	no	0;1: pulmonary atresia and tetralogy of Fallot; placement of slunt; 0;9: correction of tetralogy ofn Fallot;	no	no	ASD, multipele VSD, status post banding a. pulmonalis
Autism	no	no	no	no	no	no	no	no	no
Other	First months feeding problems, nasal resurgitation; 3;1: frustrated when is not understood, diagnosed with juvenile chronic artritis	first months swallowing problems; 0;5: immune problems, decreased number of F- and B-cells	dysmature	2;9: diagnosed with rheuma	0;0: nasal resurgitation, dysmature; immunological problems; first months failure to thrive; 0;10: EEG for epileptiform features, normal EEG; 0;11: another EEG for epileptiform features, no abnormalities	0;0: EEG for epileptiform features	first months feeding problems; immunological problems	3;0: sometimes frustration in communication; 8;0: psychiatry: diagnosed with ADHD combined type	Feeding problems during first few years

Patient	28	29	30	31	32	33	34
Non-verbal communication	1;3: 'uses a lot of signs to communicate', pointing combined with sounds; 2;5: communicates by pointin and sounds and starts making more signs, uses intonation to imitate sentences	3;2: uses supporting signs	no details	no details	2;10: tries to communicate non-verbally (for example by pulling arm)	5;2: non-verbal support in communication	2;2: communication predominantly non-verbal (touching, pulling), therapy based on supportive signs
Cleft/VPI	0;8: velum too short, no cleft	3;2: no cleft; 3;9: insufficent closure palatum molle; 4;0: surgery; 7;8: another surgery	2;9: bifid uvula, no cleft, velum lifts well	no cleft	no cleft	bifd uvula, velum seems to lift sufficiently, no cleft	no cleft, palate seems long enough to close oral cavity; 2;2: type I laryngeal fissure
Hearing problems	1;2: very sensitive to loud sounds; 4;0: tubes due to OWE, no hearing problems	3;6: AD -/- 15dB, AS normal; 4;7: both sides -/- 20-25 dB	no	no	no	6;0: seems to have problems understanding speech, request for solo-equipment in school; 6;9: audiometry AD -/- 27dB AS -/- 33 dB, prescription for hearing aids; 7;3: seems to be hypersensitive to sound,even when not wearing a hearing aid	no, recurrent otitides
test-scores	2;8: Reynell TBQ 86, Schlichting WQ 87; 3;1: SON IQ 88, SON RS 94, SON PS 84; 4;0: Reynell TBQ 86, PPVT-II-NL 88, Slichting WQ 81, ZQ 79; 4;8: Schlichting TBQ 91, WQ 83, ZQ 89; 5;6: TIQ 83	7;6: WISC-III-NL: TIQ 77, VIQ 75, PIQ 84	2;4: BSID-II-NL OI 68 (but very shy)	3;10: WPSSI-III-NL: VIQ 91, PIQ 87, TIQ 87	3;4: Reynell-test cannot be done, because child does not respond	2;11: Reynell TBQ 100, Schlichting ZQ 112, WQ 118; 5;1: WPPSI-III-NL: TIQ 82, VIQ 89, PIQ 91	7;10: WISC-III 6-17 years: TIQ 57, VIQ 59, PIQ 61
Genetic profile	no details available	no details available	unequal recombination between low copy repeats A and D of ~ 3 Mb	unequal recombination between low copy repeats C and E of ~ 1,1 Mb	no details available	unequal recombination between low copy repeats A and D of ~ 3 Mb	no details available
Cardiac problems	0;8: surgery to close VSD; 3;6: cardiac surgery	3;2: ASD type II in history	no	0;4: surgery for VSD	Tetralogy of Fallot, VSD, pulmonalis stenosis	yes (0;11: surgery)	no
Autism	4;8: features of ASS, tested, but not enough signs to diagnose autism	no	no	no	5;7: referral to child psychiatry because of suspicion PDD-NOS, has features ASS, but diagnosis cannot be confirmed	no	no
Other	Tube feeding until 0;7 ; 0;10: frequent respiratory tract infections	First months feeding problems; 3;2: frequent respiratory tract infections	1;9: child neurology because of delayed motor development and suspicion of neurological problems	premature, first years feeding problems	epileptical insults, sometimes frustration in communication	First months feeding problems (nasal resurgitation, swallowing problems); 0;11: epileptical insults, recurrent respiratory tract infections; 7;3: seems to be hypersensitive to sound,even when not wearing a hearing aid	2;2: signs of frustration in communication; no data between 2;2 and 7;10.