THE BEHAVIOURAL PHENOTYPE IN VELO-CARDIO-FACIAL SYNDROME (VCFS): FROM INFANCY TO ADOLESCENCE

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Summary: The behavioural phenotype in Velo-Cardio-Facial syndrome (VCFS): from infancy to adolescence: In this contribution the current status and recent findings of the behavioural phenotype in VCFS (22q11 deletion) are discussed with regard to motor development, cognition and neurodevelopment, and behaviour and temperament.

Motor: hypotonia in infancy, gross-motor milestones are delayed, problems with coordination and balance from preschool age on, problems with tempo/speed during adolescence.

Cognition and neurodevelopment: learning disabilities (82-100%), intellectual disability (45%), better verbal abilities than performal abilities, poor attention and concentration, visuo-perceptual-spatial problems, good (auditory) memory. An important subgroup of children (55%) has a non-verbal learning disability (NLD).

Behaviour and social-emotional development: AD(H)D, withdrawn and shy, person-dependent, social problems in relationships with peers, anxious, risk for child psychiatric problems as well as for the development of psychiatric problems during adolescence and early adulthood.

Information on the behavioural phenotype in VCFS (22q11 deletion) is of great importance to clinicians as an aid to syndrome diagnosis, but even more to parents because it offers immense direct practical value to the management of the behaviour of their child. Appropriate counseling and information on the long-term expectations, and better insight in the behaviour will lead to the development of realistic ways of coping with their child.

Key-words: Behavioural phenotype – VCFS – 22q11 deletion – Non-verbal learning disability.

INTRODUCTION

Velo-cardio-facial syndrome, also known as Shprintzen syndrome (1978), is a multiple anomaly disorder estimated to affect 1 in 4000 individuals (1). The original presenting symptoms that contributed to the clinical delineation of this entity were the association of hypernasal speech, cardiac anomalies, learning disabilities, and a characteristic facial appearance. The discovery of a submicroscopic deletion in chromosome 22q11 (9) in the majority of patients confirmed that VCFS is a specific syndrome. In most patients the deletion occurs de novo, but familial occurrence with an affected parent is noted in approximately 15% of patients (15).

The clinical phenotype of the disorder has been broadened and includes over 40 clinical features, and patients with VCFS are being identified from cranio-facial clinics, genetic clinics, pediatric cardiology clinics, learning/developmental centers, and, more recently,
also from child psychiatric units and psychiatric institutions because of behavioural and psychiatric problems.

In this contribution the current status and recent findings of the behavioural phenotype in VCFS (22q11 deletion) will be discussed.

THE CONCEPT «BEHAVIOURAL PHENOTYPE»

Behavioural phenotype is a new name for an old observation. For as long as there have been identifiable congenital causes of developmental disability, it has been recognized that people affected by some of these «syndromes», can have typical behavioural and temperamental features.

In 1994, Flint & Yule (2) gave the following definition of the concept of behavioural phenotype: «The behavioural phenotype is a characteristic pattern of motor, cognitive, linguistic and social observations, which is consistently associated with a biological/genetic disorder. In some cases, the behavioural phenotype may constitute a psychiatric disorder; in others, behaviours which are not usually regarded as symptoms of psychiatric disorders may occur». In this definition, it is not proposed that the link between behavioural phenotype and the associated biological/genetic disorder is a simple, one-to-one or universal relationship, but more likely a complex and varied one.

THE BEHAVIOURAL PHENOTYPE IN VCFS (22Q11 DELETION)

The behavioural phenotype in VCFS (22q11 deletion) will be discussed, with regard to (a) motor development, (b) cognition and neurodevelopment, and (c) behaviour and temperament.

(A) MOTOR DEVELOPMENT

Hypotonia during childhood in VCFS is reported in 76% to 85% of patients (7, 11). Already early in infancy, babies with VCFS have difficulties in developing the appropriate muscle strength and motor coordination to learn basic movements. In a previous study performed in 37 children with VCFS (14), the majority of children, — even those with a borderline to normal intelligence — were significantly slower than the normal peers in reaching the milestones «crawling» and «walking alone» (see Table 1). Most infants with a 22q11 deletion are able to walk independently between 18-24 months.

As the children grow older, the hypotonia decreases, but gross-motor abilities are often delayed. Children with VCFS have particu-
larly problems with coordination and balance. During adolescence, problems with tempo/speed are frequently observed. Graphomotor performances are also noted to be poor (4).

Physical exercises to increase muscle strength and coordination are therefore important in the care of these children, even from an early age on.

(B) COGNITION AND NEURODEVELOPMENT

Intelligence

In their initial description of the syndrome, Shprintzen et al., (10) recognized the presence of learning disabilities in all patients. Since then, learning difficulties have been reported in 82% (7) to 100% (11) of the patients with VCFS. Mental retardation or intellectual disability (not specifically defined) is reported to be present in 40% to 46%. In a previous study on 37 children and adolescents with VCFS (14), intellectual disability (defined as FSIQ < 70 or > -2 SD below the mean) was found in 45%. In the majority of them (38%) the intellectual disability was mild (FSIQ 55-69) and only two patients had a moderate intellectual disability (FSIQ 40-54). Severe mental retardation seems to be rare in VCFS. Only one child with a familial deletion and cerebellar hypoplasia was severely retarded (FSIQ 24). This study also confirmed the wide variability in intelligence in VCFS patients. Until now, there have been no good explanations for the variability in intelligence (for example, no correlation with the extent of the deletion). In our study (14) we did not find a correlation between intelligence and the presence or absence of a congenital heart defect: the mean FSIQ of children with a heart defect (n=17) was 77.2, and the mean FSIQ of the children without a heart defect (n=20) was 68, which is not statistically significant (Student's t test, p=0.10447). The mode of inheritance however, namely familial deletion versus de novo deletion, seems to play a role in the variability of intelligence in VCFS: the incidence of intellectual disability was higher in the patients with a familial deletion (10/12 or 83.3%) versus the patients with a de novo deletion (7/25 or 28%). We found a statistical significant difference in mean FSIQ between patients with a 'familial' deletion (M 63.2; SD 11.08) and patients with a «de novo» deletion (M 79.8; SD 11.8) (Student t test,

<table>
<thead>
<tr>
<th>Milestones in motor development (months)</th>
<th>Mean VCFS</th>
<th>SEM</th>
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</thead>
<tbody>
<tr>
<td>Sitting alone (8.1)</td>
<td>9.6</td>
<td>1.064</td>
</tr>
<tr>
<td>Crawling (8.7)</td>
<td>12.0</td>
<td>1.633</td>
</tr>
<tr>
<td>Standing alone (13.4)</td>
<td>13.6</td>
<td>1.208</td>
</tr>
<tr>
<td>Walking alone (14.1)</td>
<td>18.8</td>
<td>1.447</td>
</tr>
</tbody>
</table>

Table I: Milestones in motor development in VCFS (FSIQ > 70).

(a) mean (according to Bayley Developmental Scales 2-30 months).
(b) significant p<0.05.
(c) significant p<0.01.
p<0.002). In this analysis, one patient with a familial deletion and severe mental retardation was excluded. This difference can possibly be explained in part by the lower educational level of parents of familial cases versus parents of de novo cases. Indeed, parental IQ and socio-economic status, are major determining factors of the IQ in children, and here this was estimated by the educational level of the parents. In familial cases, also the parent who did not carry the deletion, had a lower educational level compared to parents of de novo cases, suggesting assortative mating.

**Neuropsychological profile**

Studies on the intelligence profile of VCFS children are scarce. In a study on 24 children and young adults with VCFS, 54% of the children had a significantly higher verbal IQ (80 ± 13) than performal IQ (72 ± 9) (8). We also found in our studygroup of 37 children and adolescents a statistical significant difference between the mean verbal IQ (M=78; SD 14.7) and the mean performal IQ (M=70; SD11.3) (14). In most children, specific cognitive deficits i.e. visuo-perceptual-spatial ability and planning ability, could be suspected from the cognitive profile. This could refer to a typical non-verbal learning disability (NLD). Recent findings of a study on primary school age children with VCFS (22q11 deletion) and a borderline to normal intelligence (FSIQ > 70), show that for many neuropsychological functions, children with VCFS (22q11 deletion) and children with NLD have the same assets and deficits (16).

Poor attention and concentration, an impulsive working style and good memory have also been described in VCFS (4, 16).

As a result of these neuropsychological assets and deficits, the majority of children with VCFS will have learning problems, especially in the areas of arithmetics and reading comprehension.

VCFS children will therefore benefit from remedial teaching and appropriate teaching strategies such as a structured learning environment or interactive computer-based instruction (6).

**(C) BEHAVIOUR AND SOCIO-EMOTIONAL DEVELOPMENT**

**Behaviour and temperament**

After the delineation of the syndrome, several common behavioural and temperamental features were observed in VCFS children, and confirmed in later studies: impulsive and disinhibited on the one hand, withdrawn and shy on the other hand (4, 13). Also ADHD, ADD, emotional instability, and anxiety have been reported during childhood (3, 4). In our experience, many children with VCFS are very attached to and dependent from the members of their family, e.g. they can not go to sleep if the mother is not at home; they only
want to stay with a babysitter if another person of the family is present (a brother or a sister); they can behave very differently depending from which person is with them: they do very well with one teacher/counselor, they underachieve with another teacher. Therefore the term «person-dependent» should be added to the list of typical behavioural features of VCFS.

In view of the reports of more severe psychopathology in older patients with a 22q11 deletion (14, 3), the most important question in this area is: what is the natural history of this behaviour, temperament and social development? To answer this question, a longitudinal study on the behaviour and social competence of infants, children and adolescents with VCFS was initiated in this Centre. Parents, teachers and adolescents were asked to evaluate the behaviour and social development of their child (or of themselves) using standardized questionnaires (CBCL, TRF, YSR) (17). These questionnaires consists of 112 behaviours (problem items). The results from the checklist are transformed first into a total problem score, second into two subscores for respectively internalising (withdrawn, somatic complaints, and anxious/depressed) and externalising problem behaviour (delinquent and aggressive), and third into a profile of clusters with specific problem behaviour (withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behaviour, and aggressive behaviour). T scores (X=50, SD=10) were calculated for each patient. For the total problem score, and the internalising and externalising subscores, a total T score of 63 or higher (90th centile or higher) is considered to be in the «clinical» range. T scores (for the separate syndromes) higher than 70 (> 98th centile) are found in populations with severe behavioural or emotional problems. For the specific problem clusters, a T score of 66 or higher (> 93rd centile) are considered to be of concern.

Until now, the study group consists of 60 children and adolescents (29 boys and 31 girls) with a 22q11 deletion. Subjects were divided into four groups based on age groups:

Group 1: infants aged 2-3 years (n=16)
Group 2: preschool children aged 4-6 years (n=19)
Group 3: primary school children aged 7-11 years (n=16)
Group 4: adolescents aged 12-18 years (n=9)

The cross-sectional data revealed the following preliminary findings:

1. Parents, teachers and adolescents report more internalizing problem behaviour than externalizing problem behaviour, and this difference seems to increase with age.
2. Over the period from preschool to adolescence, the same "quartet" of problem behaviours are reported: social problems, withdrawn, attention problems and thought problems (see figures 1.1; 1.2; 1.3). Social problems refer to problems in social relationships, especially with peers. Withdrawn behaviour points to shyness. Examples of items on the thought problems are: repeats acts, can not get mind of things, sees or hear things, strange ideas. The social withdrawal and poor social skills of children and adolescents with VCFS might result at least partly from their impaired ability to communicate with others. It might also be that neuropsychological deficits (visual-perceptual impairments, problems with new situations) contribute to their poorer social interactions skills. Also other studies (see Heine- man-De Boer et al., in this issue) have found the same combination of behavioural problems.

3. The different informants (parents, teachers and adolescents) agree on the type of problem behaviour but they disagree on the severity of the problem behaviour: parents report more social and attention problems whereas teachers report more thought problems and withdrawn behaviour. A possible explanation for the difference in reported problem behaviours between parents and teachers is that the behaviour of the child is evaluated in different environments (home versus classroom): e.g. the classroom

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**Figure 1.1:** Behavioural profile in VCFS (22q11 deletion) during preschool.

### PRESCHOOL AGE

- **Tot T**: Total T-score (total problem score)
- **Int.**: Internalising T-score
- **Ext.**: Externalising T-score
- **withdrawn**: Withdrawn behaviour
- **soc prob**: Social problems
- **thought**: Thought problems
- **att prob**: Attention problems

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Figure 1.2.: Behavioural profile in VCFS (22q11 deletion) during primary school.

Figure 1.3.: Behavioural profile in VCFS (22q11 deletion) during adolescence.
is a more structured environment than the family environment, so less attention problems, but more withdrawn behaviour because it is unfamiliar ground.

4. According to teachers, the anxious/depression syndrome significantly increases with age. During primary school, 10% of the VCFS children score within the clinical range (T-score > 70 or > 98th percentile). In puberty, this increases to 30% of the adolescents. A lot of children with VCFS are often bullied at school, even from primary schooling on. Most children have poor social skills and do not defend themselves. A possible consequence is that these children become in time more socially withdrawn and more anxious. Hormonal changes during puberty as well as a genetic predisposition to anxiety and withdrawal may play an important role in this process. An important question is whether this increase of anxiety/depression is a precursor of psychopathology in later life.

5. Over the different developmental periods, there is no statistical significant difference in behaviour between boys and girls with VCFS.

6. There appears to be a relation between the type of problembehaviour and mental level (IQ > 70 vs. IQ < 70): in the group of intellectually disabled children significantly more thought problems are found. A statistically significant (0.05 level) difference in behaviour for “thought problems” is found between the 2 groups. Parents and teachers report significantly more thought problems in the group of children and adolescents with an intellectual disability (IQ < 70). The finding of significant higher scores on “thought problems” in the group of children with an intellectual disability/mental retardation (FSIQ < 70) is not unexpected. Because of limited cognitive and verbal abilities, children and adolescents with intellectual/developmental disabilities cannot communicate their feelings and thoughts well. These children and youngsters have less coping abilities, and, when faced with difficulties, they have limited abilities to reflect, rationalize, intellectualize, and find appropriate strategies to meet their goals.

From these observations, it is clear that a good follow-up with special interest for the development of social skills and self-image of children with VCFS (22q11 deletion) is indispensable. Parents, teachers and professionals must be alert for behavioural changes, and if necessary, the VCFS child should be referred to a child/adolescent psychiatrist. Prospective, longitudinal and multi-center studies with control groups are needed to confirm these preliminary findings. For the
group of children with VCFS who are mildly to moderately intellectually disabled (FSIQ < 70), we need more appropriate instruments and questionnaires in order to get an accurate insight in the development of their behaviour and temperament.

**GENERAL CONCLUSION**

Information on the behavioural phenotype in VCFS (22q11 deletion) is of great importance to clinicians as an aid to the syndrome diagnosis, but even more to parents because it offers immense direct practical value to the management of their children's behaviours. Appropriate counseling as to what to expect, and better insight in the behaviour may lead to the development of realistic ways of coping with their child.

**REFERENCES**


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