Neuropsychopathology in 7 Patients with the 22q13 Deletion Syndrome: Presence of Bipolar Disorder and Progressive Loss of Skills

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Key Words
Behaviour · Bipolar disorder · Deletion 22q13 · Life course · Phelan-McDermid · Psychiatric disorders · SHANK3

Abstract
The 22q13 deletion syndrome is characterised by intellectual disability (ID), delayed or absent speech, autistic-like behaviour and minor, nonspecific dysmorphic features. The deletion of the SHANK3 gene is thought to be responsible for these features. In this study, the clinical data of 7 patients with the 22q13 deletion syndrome are presented, obtained by clinical genetic examination, direct behavioural observation and by interview of family members and/or caregivers, complemented by behavioural questionnaires. The specific focus was on behaviour, psychopathology and the level of functioning during life course in order to determine common features that might contribute to the delineation of the syndrome. Major findings were a high incidence of psychiatric disorders, more in particular bipolar disorder (BPD) and attention deficit hyperactivity disorder (ADHD), and a sudden deterioration after acute events, in addition to a progressive loss of skills over years. Therefore, a deletion of SHANK3 may result in a dysfunctional nervous system, more susceptible to developmental problems and psychiatric disorders on the one hand, less able to recuperate after psychiatric and somatic events, and more vulnerable to degeneration at long term on the other hand. These results are exploratory and need to be confirmed in a larger sample.

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is thought to play a significant role in the assembly of the postsynaptic density during synaptogenesis, in synaptic plasticity and regulation of dendritic spine morphology [Boeckers et al., 2002].

This study presents the clinical data of 7 patients with the 22q13 deletion syndrome, obtained by clinical examination by a clinical geneticist, direct behavioural observation, and by interview of family members and/or caregivers, complemented by behavioural questionnaires. The main focus was behaviour, psychopathology and the level of functioning during the life course, in order to determine common features that might contribute to the delineation of the syndrome.

Materials and Methods

Study Population

Over the last 6 years, almost 4,000 patients with intellectual disability (ID) underwent a diagnostic full genome array at the Centre for Human Genetics of the University Hospitals Leuven, Belgium. Informed consent was obtained from the parents or legal guardians of the affected patients and their healthy family members. Genomic DNA was extracted from peripheral leukocytes of EDTA-treated blood according to standard procedure guidelines. The genomic DNA of the patients was either screened using the BAC/PAC-array [Menten et al., 2006] or the Oxford Gene Technology (OGT) CytoSure™ ISCA oligoarray set (Oxford Gene Technology, Oxford, UK) containing either 105k or 180k DNA oligonucleotides with a minimum resolution of 200 kb. All genome coordinates were according to NCBI human genome build 37 (hg19, February 2009).

In 7 patients, a 22q13 microdeletion was identified. In 1 patient (patient 7), an additional small copy number variation of 31 kb of unknown significance at 5q35.3 was also detected. The ages of the patients range from 5 to 51 years, and 3 patients were male, 4 female. All patients were examined at one or more occasions by an experienced clinical geneticist. Medical history was obtained from the parents, grand-parents, care-givers, and referring physicians. If parental DNA was available, array comparative genome hybridisation or FISH was performed to determine whether the deletion was inherited or not.

Observation and Questionnaires

All patients were directly observed in their everyday environment by 2 observers during at least 1 h. Parents and/or caregivers were also interviewed to obtain data regarding the developmental course, former and present level of functioning, medical and psychopathological history. In addition, adaptive functioning, autism spectrum symptoms and psychopathology in all 7 individuals were assessed by questionnaires. Family members and/or caregivers completed the Dutch versions of the Vineland Adaptive Behaviour Scale for individuals with ID (VABS, Vineland-Z) [de Bildt and Kraijer, 2003], the Scale of Pervasive Developmental Disorders in Mentally Retarded Persons (PDD-MRS) [Kraijer and de Bildt, 2005] and the Developmental Behaviour Checklist (DBC) [Einfeld and Tonge, 1995].

The Vineland-Z includes 225 items, divided in 3 domains: communication (67 items), daily living skills (92 items) and socialisation (66 items). In each domain, the items are ranked by level of difficulty in developmental order. Scores are determined by means of an open-ended interview with the personnel as respondents. Item-scores (2, 1 or 0) are calculated per domain in which they indicate the following: 2 = behaviour is usually performed, 1 = behaviour is sometimes or partly performed, 0 = behaviour is not performed. The Vineland-Z total score includes the 3 separate domain-scores.

The PDD-MRS is a simple classification and screening instrument for identification of autistic disorders (of the entire spectrum) in persons with ID ranging from mild to profound with an age-range of 2–55 years.

The DBC is a validated measure of psychopathology in young people with ID. Each item is rated as follows: not true, somewhat true or very true. Information from a Total Behaviour Problem Score and 5 sub-scales (self-absorbed, disruptive, communication disturbance, social relating and anxiety) was analysed.

Results

The overview of the clinical and molecular data is presented in table 1. There were no peculiarities during pregnancy, birth or neonatal period. Except for patient 3, each individual was able to walk independently before the age of 18 months. In all patients, language development was severely retarded (first words between 2 years and 6 months and 6 years). Currently, all function at a severe to profound level of ID. Five are in residential care, the 2 youngest attend special education and live in their home environment, combined with semi-residential care. All of them attended special education, and none are able to work in a sheltered environment.

Patient 2 inherited the deletion from her mother; this 36-year-old mother with a moderate ID had normal early motor milestones, and her early language milestones were not markedly delayed either. At present, she is able to construct elementary sentences, works in a sheltered environment and needs major assistance from her parents to take care of her daughter. There is no history of somatic or psychiatric problems.

The results of the questionnaires regarding the 7 observed patients are summarized in figures 1 and 2, and table 2.

In figure 1, the DBC-profiles of all 7 patients with a del22q13.3 are shown. All individuals show severe challenging behaviour; all have a total problem score between Pc. 75–90. Most prominent problem behaviours are self-absorbed behaviour, problems with social relating and disruptive behaviour. In 1 individual (patient 5), anxiety is the most problematic.
Table 1. Overview of clinical characteristics and developmental data

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>5 yrs 9 mo</td>
<td>6 yrs 10 mo</td>
<td>17 yrs 8 mo</td>
<td>24 yrs 9 mo</td>
<td>43 yrs 10 mo</td>
<td>46 yrs 6 mo</td>
<td>51 yrs 11 mo</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Family history</td>
<td>negative</td>
<td>both parents moderate ID</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>limb defects in brother and brother of maternal grandfather</td>
</tr>
<tr>
<td>Inheritance</td>
<td>de novo</td>
<td>maternally inherited</td>
<td>de novo</td>
<td>de novo</td>
<td>parents NT, sibs normal</td>
<td>parents NT, sibs normal</td>
<td>NT</td>
</tr>
<tr>
<td>Deletion size</td>
<td>49.28±1.146–49.50±1.571</td>
<td>199 kb</td>
<td>49.42±1.03–49.56±.789</td>
<td>76 kb</td>
<td>49.47±1.36–49.56±1.789</td>
<td>97 kb</td>
<td>47.74±1.34–49.56±.810</td>
</tr>
<tr>
<td>Gene content</td>
<td>SHANK3 + 11 other genes</td>
<td>SHANK3, ACR, RABL2B</td>
<td>SHANK3, ACR, RABL2B</td>
<td>SHANK3, ACR, RABL2B</td>
<td>SHANK3, ACR, RABL2B</td>
<td>SHANK3, ACR, RABL2B</td>
<td></td>
</tr>
<tr>
<td>Array platform</td>
<td>OGT 180K</td>
<td>OGT 105K</td>
<td>OGT 105K</td>
<td>OGT 180K</td>
<td>OGT 180K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysmorphism</td>
<td>–</td>
<td>strabismus</td>
<td>coarse face, full lips, deep-set eyes, straight eyebrows, low-set ears, hypotonic posture, joint hyperlaxity, clubfeet</td>
<td>–</td>
<td>hypotonic face, kyphoscoliosis, cutaneous syndactyly fingers 3 and 4, finger swanling, wrist dorsiflexion, thumb adduction</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Growth parameters</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age</td>
<td>5 yrs 1 mo</td>
<td>17.7 (P25)</td>
<td>105 (P10)</td>
<td>52 (P75)</td>
<td>15 yrs</td>
<td>24 yrs</td>
<td>37 yrs</td>
</tr>
<tr>
<td>OFC (cm)</td>
<td>52 (P75)</td>
<td>49.9 (P25)</td>
<td>54.5 (P25)</td>
<td>54.7 (P50)</td>
<td>52 (P10–25)</td>
<td>158 (P10)</td>
<td>54 (P25–50)</td>
</tr>
<tr>
<td>Somatic diagnoses/age</td>
<td>–</td>
<td>eczema, drop attacks of unknown etiology</td>
<td>–</td>
<td>Crohn’s disease/28 yrs, metrorraghia</td>
<td>mumps encephalitis/18 mo, NMS/27 yrs, DVT/34 yrs, septic shock/40 yrs</td>
<td>epilepsy, epileptic state/45 yrs, gastric reflux</td>
<td></td>
</tr>
<tr>
<td>Neuroimaging/age</td>
<td>–</td>
<td>MRI/2 yrs 8 mo: normal</td>
<td>MRI/22 mo: normal</td>
<td>MRI/9 yrs: normal</td>
<td>CT/19, 25, and 41 yrs: corticobasal atrophy</td>
<td>CT/19, 30 yrs: normal</td>
<td>CT/43 yrs: mild corticobasal atrophy</td>
</tr>
<tr>
<td>Developmental testing/age</td>
<td>BSID/25 mos: 11.5 mo</td>
<td>BSID/25 mos: 15 mo</td>
<td>BSID/25 mos: 16 mos</td>
<td>BSID/3 yrs 10 mos: 3 mos</td>
<td>IQ/7 yrs: ± 50</td>
<td>IQ/7 yrs: 18</td>
<td></td>
</tr>
<tr>
<td>Language testing/age</td>
<td>NNST/26 mos: R+E &lt;12 mo</td>
<td>NNST/26 mos: 1 yr</td>
<td>Reynolds/3 yrs 4 mos: R: 2 yrs 9 mo</td>
<td>Terman IQ 39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor testing/age</td>
<td>PDMS/26 mos: 18 mo</td>
<td>PDMS/26 mos: 15 mos</td>
<td>Reynell/9 yrs 5 mos: R: 3 yrs 6 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive loss of skills</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Current level of functioning</td>
<td>ID Language</td>
<td>severe short sentences walking</td>
<td>severe single words walking</td>
<td>profound no speech walking</td>
<td>severe single words walking</td>
<td>profound no speech</td>
<td>profound no speech</td>
</tr>
<tr>
<td>Motor function</td>
<td>walking</td>
<td>walking</td>
<td>walking</td>
<td>wheelchair bound</td>
<td>wheelchair bound</td>
<td>bedridden</td>
<td>bedridden</td>
</tr>
</tbody>
</table>

Neuropsychopathology in 7 Patients with the 22q13 Deletion Syndrome
Figure 2 shows the Vineland-Z profiles of all 7 patients with a del22q13.3. In 6 out of 7 patients, communication is very poor, and 5 out of 7 have prominent problems within the domain of socialisation. Daily living skills seem to be well developed in 5 out of 7 patients.

In table 2, the total PDD-MRS score of all 7 patients is reported. Four individuals have a score within the PDD-spectrum: most typical for these patients are the unpredictable outbursts, stereotypic behaviours (clapping, biting) and obsessive traits.

Although all individuals have always shown autistic-like behaviour, like low or absent social reciprocity, poor nonverbal skills, stereotypic behaviour and rigidity, none have been specifically examined and assessed for autism. This is probably due to the severe to profound level of ID. Our observations and gathered data indicate that the criteria for a diagnosis of PDD may be fulfilled in several individuals.

Four patients have been evaluated by a psychiatrist. Due to extreme overactive and impulsive behaviour with a very short attention span, patient 2 was diagnosed with ADHD, responding well to treatment with methylphenidate. Four others (patients 4, 5, 6, and 7) received a formal diagnosis of bipolar disorder (BPD) because of the presence of at least one manic episode with irritable mood, psychomotor agitation, decreased need for sleep, and increased speech (in-
increased babbling and talking). The latter was unexpected because these patients otherwise did not talk.

Remarkably, many patients show a progressive loss of skills during their life. This is the most subtle in the 2 youngest children, with regard to language skills, e.g. losing acquired words when they are no longer practiced. The other individuals also showed deterioration in language over years, like a decline in receptive and expressive language or a regression in pronunciation. Several other developmental domains are also affected. Concerning gross and fine motor skills, parents, caregivers and therapists observed, for instance, deterioration in balance and coordination, progressive rigidity of the posture with shuffling gait, loss of the ability to do handwork, and to eat with a knife and fork. With regard to social skills, a reduced eye-contact and diminished social interest were perceived.

In addition, several patients showed severe and sudden loss of skills after acute events which could not always be regained.

Patient 4 was diagnosed with a BPD, rapid cycling type with psychotic symptoms. The response of neuroleptics and benzodiazepines to the excessive mood and activity swings was poor, thus requiring higher doses. Due to a rise in temperature and the fear of a neuroleptic malignant syndrome, the neuroleptics were stopped. Few days later, she was hospitalized for a day because of a sudden blood pressure fall with decreased consciousness, presumably because of an overdose of benzodiazepines. This was immediately followed by an apathetic and catatonic period, in which she stopped moving and talking. Afterwards, her level of functioning had become very different than before. She was not able to use the language she

Fig. 1. DBC-profiles in del22q13.3 (n = 7).

Fig. 2. Vineland-Z profiles in del22q13.3 (n = 7).
knew, stopped interacting with others and did no longer recognize her mother. The mood swings became even more explicit than they had been before. She stopped eating independently and also lost continence.

Patient 6 was hospitalized in intensive care for a malignant neuroleptic syndrome during a substantial manic episode at the age of 27, treated with high doses of haloperidol. Afterwards, he lost the ability to walk or eat independently, needing a long period of rehabilitation to recover. At 40 years, he was hospitalized again for septic shock due to aspiration pneumonia. Thereafter, he lost even more skills (loss of active and passive language, loss of walking, independently eating and dressing, and loss of continence) that could not be regained at all. Currently, he is spastic and wheelchair bound.

Patient 7 became totally dependent and bedridden after a prolonged epileptic state.

**Discussion**

At present, the psychiatric disorder the most frequently associated with the 22q13 deletion syndrome is autism. In our patient sample, all individuals show autistic-like behaviour and 4 patients have a PDD-MRS-score that falls within the PDD-spectrum. However, the most remarkable findings in our study are the high incidence of another psychiatric disorder, namely BPD, together with progressive loss of skills.

**Bipolar Disorder**

Surprisingly, 4 out of a group of 7 individuals (including 2 young children) were diagnosed with BPD. The diagnosis of paediatric BPD still remains controversial because the clinical presentation of mania in children and adults can be very distinct. Furthermore, the high incidence of comorbid disorders complicates the diagnostic process because of the significant symptom overlap in children. Due to the fact that clinicians are often more familiar with the clinical presentation of the comorbid disorder, like for instance ADHD, some presume that a considerable part of the children diagnosed with ADHD might actually have BPD or an unrecognised comorbid BPD [Youngstrom et al., 2005].

If in our group only the adults are taken into consideration, the incidence of BPD is very high (4 out of 4 patients). One of the children (patient 2) is diagnosed with ADHD. She doesn’t show manic episodes, but her further development and behaviour should be carefully monitored.

Presently, only little data regarding mood disorders in patients with 22q13 deletion syndrome are available in the literature. However, BPD has been associated with several chromosome regions, amongst others 22q13 [Kato, 2007]. In this region, 2 potential BPD candidate genes, *MLCI* and *BRDI*, were put forward. The *MLCI* gene is expressed in brain and encodes a putative nonselective cation channel. It is presumed to modulate neuronal functions [Verma et al., 2005]. *BRDI*, also expressed in brain, is considered a potential regulator of transcription with a presumed role in neurodevelopment [Severinsen et al., 2006]. In our group of bipolar patients, the deletion in patient 5, 6 and 7 involves beside SHANK3 also *MLCI* and *BRDI*. However, in patient 4, the latter genes are not deleted, suggesting a possible role for SHANK3 in this disorder. This is in agreement with a previous finding where a patient with a ring chromosome 22 was described with a rapid cycling BPD [Sovner et al., 1996]. Although no further molecular studies were done in this patient, it is likely that SHANK3, due to its subtelomeric position, is deleted.

**Loss of Skills**

Another remarkable observation is the loss of skills in many of our patients. This regression is the most apparent in the oldest patients and occurs most dramatically after acute events, such as a septic shock, epileptic state, catatonic phase, or malignant neuroleptic syndrome. A similar severe neurological deterioration was observed in 2 individuals with epilepsy over 40 years in a group of 44 patients with the 22q13 deletion syndrome, and SHANK3 haploinsufficiency was considered as responsible for this [Bonaglia et al., 2011].

This raises the interesting question whether the deterioration in our patients is a consequence of acute incidents or less acute underlying pathology like BPD, or whether it might also be inherent to the 22q13 deletion syndrome. The latter may be the case since some of these patients already showed a progressive loss of functioning decennia before the acute deterioration. Furthermore, the loss of functioning is also reported in the patients with an uneventful clinical course. It is even noticeable, though in a more subtle manner, in the youngest patients, suggesting an onset during childhood. This observation might suggest a direct relation between the neurological deterioration and the SHANK3 deletion in the Phelan-McDermid syndrome. It might be possible that haploinsufficiency of SHANK3 renders the nervous system more vulnerable to degeneration on long term and less capable to recuperate after psychiatric and somatic events.
Strengths and Limitations of This Research

This research has several strengths. First, we were able to gather retrospective data in addition to data regarding the current level of functioning of our patients, and this enabled us to recognize the degenerative processes. Furthermore, we had direct contact with parents and caregivers besides the use of questionnaires. Moreover, the direct observation of the patients by 2 behavioural scientists led to a better understanding and interpretation of the data obtained by the interview and questionnaires.

The most important limitation of this research is the size of our sample, too small to draw firm conclusions. Second, the large age differences render the interpretation and comparison of data more difficult. Third, diagnostics are made by different psychiatrists at different moments. However, the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM) have been used [APA, 2001].

Directives for the Future

First, in clinical practice, the possibility of a 22q13 deletion needs to be considered in severe to profound intellectually disabled individuals not only with autistic-like behaviour, but also in individuals with ADHD or ADHD-like behaviour, bipolar disorder, or loss of skills. Second, in patients with a known 22q13 deletion syndrome, caregivers need to be vigilant for the emergence of psychiatric symptomatology in general and for the development of BPD in particular. Third, continuously practising acquired skills might maintain them for a longer period of time, and rigorous medical follow-up seems important to prevent severe pathology that could lead to an acute loss of functioning.

Because of the lack of specific dysmorphic features in the 22q13 deletion syndrome, future research to delineate the phenotype should also focus on behavioural and psychiatric aspects. Therefore, larger groups of 22q13 deleted patients need a systematic and longitudinal psychiatric assessment. Moreover, closer investigation should demonstrate whether SHANK3 might be a possible candidate gene for BPD and whether the degeneration is part of the phenotype.

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References


