RELEVANCE OF DELETION BREAKPOINT SPECIFICATION IN 22q11.2 DELETION SYNDROME: CLINICAL MANAGEMENT OF THREE ILLUSTRATIVE PATIENTS

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Abstract

Objective: One of the most prevalent deletion syndromes is the common 22q11.2 deletion syndrome (22q11.2DS) that has a highly variable somatic and behavioural phenotype with different levels of intellectual disability and a variety of congenital abnormalities. Nowadays, in addition to the common deletion, three subtypes are distinguished based on the breakpoints of the deleted 22q11.2 region, the proximal and central deletion within the common deletion, and an additional distal deletion in 22q11.2. The involved region determines not only the somatic anomalies, but also seems to play a role in the behavioural and psychopathological presentation.

Method: From a group of 35 patients with genetically proven 22q11.2DS and a record with extensive information on somatic, neuropsychiatric and neuropsychological data, for each deletion subtype, the patient with the most comprehensive dossier was selected. Their detailed case vignettes were analyzed as to the differences in psychopathology and treatment.

Results: The common 22q11.2 deletion (involving both the proximal and central part) was dominated by a great variety of somatic anomalies and symptoms form the psychotic and mood spectrum, whereas the distal 22q11.2 deletion mainly showed congenital cardiac defects and anxiety bound psychopathology. In the central 22q11.2 deletion variant, autistic behaviours formed the core symptoms. In the common deletion, an atypical antipsychotic in combination with a mood stabilizer appeared to be most effective while an antidepressant agent induced long lasting effectiveness in the distal variant. The central variant typically presented with symptoms from the autism spectrum that did not warrant psychotropic intervention.

Conclusions: The 22q11DS deletion region is of relevance for the range of somatic investigations and the assessment of differentiated psychopathology and may provide guidance for the treatment regimen.

Key words: 22q11.2 deletion syndrome, low copy repeat region, psychopathology, differential psychopharmacology, contextual neuropsychology

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Introduction

The 22q11.2 deletion syndrome (22q11.2DS; OMIM #188400 and #192430), also called Shprintzen syndrome, DiGeorge syndrome or Velo-Cardio-Facial Syndrome (VCFS), is a multisystem disorder characterized by a highly variable phenotypical presentation and a wide IQ-variability ranging from mild-moderate intellectual disability to normal intelligence. The deletion syndrome is mostly caused by a ~3 Mb deletion which is flanked by low copy repeats (LCRs) LCR22-A to LCR22-D, encompassing the HIRA, TBX1 and COMT genes which, among others, are considered to be crucial for the clinical phenotype. This so called common deletion is strongly associated with a diversity of congenital anomalies, particularly vascular and renal malformations as well as immunodeficiency due to thymic hypoplasia and dysfunctions of thyroid and parathyroid. In a small percentage of patients with this type of deletion early-onset Parkinson disease occurs (Butcher et al. 2013). In addition, several types of seizures may be present (Strehlow et al. 2016). Within the common 22q11.2DS a distinction can be made between (a) the less frequent...
central variant located between LCR22-B and LCR22-D comprising the SERPIND1, LZRT1, and CRKL genes, and (b) the proximal variant (LCR22-A to LCR22-B) encompassing the HIRA, TBX1, and COMT genes. The former rather than the latter is predominantly associated with renal and urogenital anomalies and to a lesser extent with cardiac malformations (Rump et al. 2014).

In addition to the proximal and central variant, also, a 22q11.2DS variant is described that is caused by a deletion distal from the common deletion (distal of LCR22-D i.e., LCR22-D to LCR22-E, LCR22-F or LCR22-G). This distal variant may comprise the MAPK1, BCR, SMARC1, and SPECIIIL genes, has a generally mild phenotypical presentation and is typically associated with cardiac anomalies, including conotruncal defects in the absence of other relevant somatic dysfunctions (Fagerberg et al. 2013, Bengoa-Alonso et al. 2016). The different subtypes of 22q11.2DS with their LCRs are depicted in figure 1. Given the multisystem condition of the 22q11.2DS, Fung and colleagues published in 2015 practical guidelines for managing adults with this condition.

Not only regarding somatic anomalies but also with respect to psychopathology, there is some evidence that the above mentioned 22q11.2DS subtypes may also be accompanied by a differential neuropsychiatric profile (Burnside 2015, McDonald-McGinn et al. 2015, Hachhamdioglu et al. 2015). In the following, the putative phenotypic variability will be illustrated by means of concise case vignettes of three patients in whom, dependent on the involved LCR-region, a common, distal or central 22q11.2 deletion was demonstrated. Results will be discussed in terms of specific psychopathological characteristics and in relation to the impact of psychopharmacological intervention.

Method

Over the past years a total of 35 genetically proven 22q11DS patients were referred for diagnosis and treatment of recurrent psychiatric symptoms. In 31 patients, a common 22q11.2 deletion (LCR22-A to –D) was detected (female: n=17; male: n=14; age range 16-70 years). In three patients, a distal deletion was present (LCR22-D to –E: patients DE1 and DE2 in figure 1; and one LCR22-E to –F: patient EF in figure 1). In one patient, a central 22q11.2 deletion was demonstrated (LCR22-B to –D: patient BD in figure 1). Two out of the patients with a common deletion (male: 45 years; female: 48 years) had an additional diagnosis of early Parkinson disease. Part of this group has been published before in a study on the psychopharmacological treatment of 22q11.2DS related psychoses (Verhoeven and Egger 2015). In all patients, a standard neuropsychiatric examination was performed using among others the elements of the Comprehensive Psychopathological Rating Scale (CPRS; Åsberg et al. 1978, Goekoop et al. 1994) and following the format of the DC-LD (Royal College of Psychiatrists 2001). Where possible, intelligence as well as cognitive and social-emotional functioning was assessed by means of validated instruments. In addition, relevant data from all available sources about treatment history and behavioural repertoire were collected. Upon indication, the diagnostic procedure was extended with somatic, neurological or neuropsychological examination.

From this group of patients, for each deletion subtype, the most complete case record was selected and the resulting three patients (AD, DE2 and BD in figure 1) were described in detail with respect to their differences in behavioural and psychiatric history as well as in psychopathology and (pharmacological) treatment response.

Results

Differential psychopathology

The psychopathological phenotype associated with a common deletion was typified by a history of relapsing schizophrenia-like psychosis, partial non-response to conventional antipsychotics as well as by mood instability and diminished social-emotional functioning. Anxieties and mood instability were manifest as well. The patient with a distal deletion predominantly showed anxiety symptoms as well as a cognitive profile characterized by deficits in problem solving/planning and in abstract and social thinking. The behaviour of the patient with a central deletion was characterized by symptoms from the autism spectrum only.

Case vignettes

1. Common 22q11.2 deletion (AD)

The patient is a 48-year-old female born to non-consanguineous parents and has one healthy, younger brother. Pregnancy and delivery were unremarkable. Early infancy was characterized by feeding problems, delayed milestones, especially speech and language due to velopharyngeal insufficiency, and recurrent upper airway infections. She followed special education. To velopharyngeal insufficiency, and recurrent upper airway infections. She followed special education.

Despite a great variety of antipsychotics while valproic acid was continued. At discharge to a sheltered home facility, a diagnosis of reactive psychosis was made and treatment comprised valproic acid and bromperidol. During subsequent years, several psychotic relapses occurred characterized by paranoid ideation, auditory hallucinations, mood instability with intermittent ideas of grandiosity, crying, and an increase of pre-existent challenging aggressive behaviours. Since antipsychotics (bromperidol, levomepromazine, sulpiride, haloperidol) provided no further amelioration, from the age of 30 years extensive assessments were performed. CT-brain and echo abdomen disclosed no abnormalities whereas echo heart demonstrated a borderline enlargement of the thoracic aorta. In addition, hypoparathyroidism was diagnosed as well as psoriasis inversa/pustulosa. FISH analysis with a probe specific for the HIRA region disclosed a de novo deletion in 22q11.2. Treatment comprised 200 mg sulpiride, 2 mg haloperidol, 1000 mg valproic acid, 2 µg alfalcacidol and 1500 µg calcium/cholecalciferol. Two years before the present referral, psychological assessment was performed that disclosed mild intellectual disability with WISC-III total intelligence and VABS/ESSEON socio-emotional functioning corresponding with an age of 7.2 years and 2.6 years, respectively.

The patient was referred because of increasing challenging behaviours with great impact on her care.
givers and to re-evaluate psychopharmacological treatment. Since the etiological diagnosis was established with FISH only, first genome wide array analysis was performed to further characterise the 22q11.2 deletion. A de novo 2.88 Mb interstitial deletion was found in 22q11.21 flanked by LCR22-A and lcR22-d, corresponding with a common 22q11.2 deletion. Somatic, neurological, neuropsychological and laboratory investigations did not show any new viewpoints. After adjustment of psychotropics to finally 30 mg aripiprazole in combination with 1000 mg valproic acid and implementation of syndrome-specific guidance by the care givers, apart from incidental context driven referential thinking, behaviour and mood significantly stabilized.

2. Distal 22q11.2 deletion (DE2)

The patient is a 17-year-old female, prematurely born after 35 weeks of gestation and is the only child of non-consanguineous, healthy parents. Postnatally, major ventricular and minor atrial septal defects and patent ductus arteriosus were diagnosed for which she underwent surgical correction shortly thereafter. Development was characterized by feeding problems and recurrent upper airway and urinary tract infections that necessitated hospitalizations. Also, delayed milestones were noticed with clumsy motor functioning for which physical therapy was given. Aged eight, anxieties, in particular when separated from the mother, and difficulties in falling asleep developed. Psychological assessment at that time showed borderline intellectual functioning with difficulties in planning, concentration, and calculation as well as impaired visuospatial perception. As a consequence, she followed special education. Over subsequent years, although her peer interactions were relatively normal, she was frequently bullied and increasingly reported severe anxieties and panic attacks upon which she was referred.

At examination, it became apparent that severe anxieties, mood instability, and irritability were typically related to stressful events and coincided with vague paranoid ideation and preoccupations with death. In addition, the patient complained about negative self esteem and lowered mood. Physical examination revealed small stature, nasal speech and minor facial dysmorphisms. All laboratory tests were normal and MRI/mRa scanning of the brain revealed no structural or vascular abnormalities. Detailed neuropsychiatric evaluation disclosed anxieties, affective instability, mood swings, mild perseverations, ideas of reference and some paranoid ideation as well as social withdrawal and impaired social skills. Neuropsychological assessment showed a WAIS-III Total IQ of 81 (VIQ: 76; PIQ: 88), poor attention and concentration without memory impairments, and mild executive dysfunctions (switching, inhibition, and planning). As to personality, low self esteem, limited social autonomy, as well as enhanced suggestibility and sensitivity to external stimuli were noticed.

Based on her developmental and somatic history, extensive etiological investigation was performed that ultimately resulted in the detection of a de novo 740 kb loss in 22q11.21q11.22 containing 14 known genes including MAPK1 and flanked by LCR22-D and LCR22-E, corresponding with a distal 22q11.2 deletion. Given the findings on behaviour and psychopathology, a diagnosis of anxiety disorder, more specifically, panic disorder was made. The patient was

Legend to figure 1

Overview of the 22q11.2 region with the Low Copy Repeats (LCR22) and selected genes shown, the different subtypes of deleted regions indicated by the horizontal arrows and the described patients by horizontal rectangular blocks. At the department of human genetics of the Radboud University Medical Center in a 10-year time frame (2007-2017), a recurrent copy number gain or loss in the 22q11.2 region was detected by genome wide array analysis in 173 index patients, involving 55 duplications and 118 deletions. Of the deletions, 98 were common (LCR22A-D) of which eight proximal (7%; LCR22-A-B). In addition, nine were central (8%; LCR22B-D) and 11 distal (9%; with breakpoints between LCR22D- and LCR22-H).
subsequently treated with citalopram in a daily dose of 20 mg. In addition, psychosocial supportive therapy was given. Follow-up over a period of more than five years, maintenance therapy with citalopram had led to full remission of symptoms of anxiety disorder and stabilization of mood. As a consequence, she was able to adequately engage in structured and manageable working activities.

3. Central 22q11.2 deletion (BD)

The patient is an intellectually disabled 12-year-old boy, born to non-consanguineous parents. He has one older, healthy sister. Because of central hypotonia, feeding problems, recurrent upper airway infections, delayed developmental milestones and impaired speech and language, medical day care followed by special education was necessary. At the age of nine years, he underwent neurological examination after experiencing complex partial seizures and a single tonic-clonic one. Treatment with levetiracetam was started that was, however, stopped by his parents because of serious behavioural side effects like aggression and agitation. Because of severe eating problems, he was referred for pediatric examination that, apart from growth delay (height: 124.7 cm, -2.1 SD; weight: 20.2 kg, -2.1SD) and psychomotor retardation, demonstrated no somatic abnormalities. EEG-registration, MRI brain and echo kidneys were all normal. By means of MLPA technique, a 22q11.2 deletion syndrome was demonstrated. One year later, a diagnosis of autism spectrum disorder was made.

He was referred for analysis of progressive challenging behaviours and persistent eating problems. As to the etiological diagnosis, genome wide array analysis was performed for further characterisation. A de novo 1.08 Mb deletion in 22q11.21 flanked by LCR22-B and LCR22-D was found corresponding with a central 22q11.2 deletion. Neuropsychological testing disclosed moderate intellectual disability (RAKIT-2 Total IQ: 56). Developmental age was estimated to correspond with about six years with relative deficiencies in social and adaptive functioning. Attention, memory and executive functioning were in line with the level of intelligence. ADOS-2 classification yielded a diagnosis of autism (total score 21; cut off: 9). The combination of findings is in agreement with the central 22q11.2 behavioural phenotype characterized by an autistic profile in the absence of major congenital anomalies. Apart from psycho-education to his parents and day-time care givers as well as the implementation of contextual measures, no specific pharmacological treatment was advised.

Discussion

In the patient with a common 22q11.2 deletion, symptoms from the psychotic and mood spectrum dominated the clinical picture whereas in the patient with the distal 22q11.2 deletion anxieties formed the primary psychopathological manifestation. The patient with the central 22q11.2 deletion showed a symptom profile that typically pointed at a disorder within the autism spectrum. These observations strengthened the presence of a differential psychopathological phenotype according to the deleted 22q11.2 region. As reported earlier (Verhoeven and Egger 2015), in patients with a 22q11.2 deletion, contextual measures matching the individual's neuropsychological profile are warranted, a fortiori in those with a common or a central deletion. From the literature it has become obvious that in patients with the common 22q11.2DS, a specific neuropsychological phenotype is present characterized by impaired visuospatial ability and a diminished comprehension of abstract and symbolic language (Verhoeven et al. 2007, Furniss et al. 2011, Kates et al. 2015, Maeder et al. 2016), whereas the distal 22q11.2DS may be associated with enhanced suggestibility and sensitivity to external stimuli without disturbances in social cognition (Verhoeven et al. 2011, Fagerberg et al. 2013). Apart from a behavioural profile characterized by autistic traits, so far no specific neuropsychological phenotype is described in patients with a central 22q11.2DS.

It is well known that the common 22q11.2DS, especially the proximal subtype (LCR22-A to -B, comprising the COMT gene) is highly associated with schizophrenia-like psychoses and affective disorders (Squarcione et al. 2013, Schneider et al. 2014, Tang et al. 2014, Kates et al. 2015, Van et al. 2017). Case studies have suggested that the atypical antipsychotics quetiapine and clozapine, and perhaps also aripiprazole, often in combination with the mood stabilizing agent valproic acid, are most effective (Verhoeven and Egger 2015, Butler et al. 2015). For the treatment of anxiety disorders as observed in the patients with a distal 22q11.2DS, the SSRI citalopram seems to be the most appropriate choice (Verhoeven et al. 2011). In this respect, the MAPK1 gene, although not known to be a disease gene, may still be involved in the vulnerability to mood and anxiety disorders (Fagerberg et al. 2013, Antypa et al. 2016). For patients with a central 22q11.2DS, no specific psychopharmacological treatment is available.

In conclusion, subtyping of 22q11.2DS according to the flanking LCRs may provide guidance not only to determine which additional somatic, endocrine or neurological examinations have to be performed with their potential therapeutic consequences, but also to address the differential psychopathology in order to achieve a balanced choice of neuropsychological and psychopharmacological interventions that has the greatest chance for a long lasting effective treatment with the lowest risk for unwanted side effects.

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