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Neurocognitive profile and onset of psychosis symptoms in children, adolescents and young adults with 22q11 deletion syndrome: A longitudinal study

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ABSTRACT

Background: The neurobehavioral phenotype of 22q11.2 deletion syndrome (22q11DS) includes cognitive dysfunction and high rates of psychotic symptoms and schizophrenia.
Existing research has mainly considered changes in IQ, especially its decline, as a psychosis predictor. The aim of this study was to investigate, in a longitudinal perspective, the relationship between neuropsychological abilities (not only IQ but also executive functioning, language and visual-motor integration abilities) and onset of psychotic symptoms in a sample of children, adolescents and young adults with 22q11DS.
In addition, the role of comorbid psychiatric disorders at baseline was taken into account.
Methods: 75 participants with 22q11DS, aged between 6 and 27 years at baseline, were included. Eighteen of the 75 participants had developed psychosis at the one year follow-up (onset psychosis-OP) and constituted the first group; 57 participants who had not developed a psychosis at the one year follow-up (without onset psychosis-WOP) constituted the second group.
Results: At baseline, group OP showed lower IQ (both full scale and verbal and performance scale) and more perseverative errors as well as a reduced number of correct categories on the Wisconsin Card Sorting Test (WCST) compared to group WOP. In addition, at baseline, group OP showed a higher frequency of depressive disorders than group WOP.
Conclusion: Even if with caution, results suggest neuropsychological deficits and depressive symptoms should be considered and monitored as possible clinical signs for the onset of psychosis in children, adolescents and young adults with 22q11DS.

1. Introduction

22q11.2 deletion syndrome (22q11DS), originally known as velocardiofacial syndrome or DiGeorge syndrome, is a genetic syndrome (Schneider et al., 2014a; Scambler et al., 1992) associated with microdeletion of the chromosome 22 band q11 with an estimated prevalence varying between 1 per 3000 to 1 per 6000 live births (McDonald-McGinn and Sullivan, 2011). The physical and neurobehavioral phenotype of the syndrome includes high rates of congenital dysmorphic features (Bassett et al., 2001; McDonald-McGinn and Sullivan, 2011), structural brain abnormalities (Chow et al., 1999), cognitive dysfunction (Vorstman et al., 2015; Antshel et al., 2010), and high rates of psychiatric disorders (Gothelf et al., 2008), in particular schizophrenia (Murphy, 2005; Schneider et al., 2014a).

The cognitive profile in individuals with 22q11DS varies over the course of development and is highly variable between individuals (Schneider et al., 2014a; Armando et al., 2013). However, there are some replicated patterns. The majority of individuals with 22q11DS have an intellectual ability that falls in the borderline range (IQ 70–84), about one-third present mild intellectual disability, while more severe intellectual disability is uncommon (Bassett et al., 2005; Chow et al., 2006; Swillen et al., 2000). In early childhood, children with 22q11DS show non-verbal learning deficits and performance IQ tends to be significantly lower than verbal IQ (De Smedt et al., 2009; Jacobson et al., 2010; Swillen et al., 1999). However, data seem do not support the distinction between performance and verbal IQ scores in adolescence (Antshel et al., 2010; Green et al., 2009).

Concerning predictive factors of later psychotic onset in individuals with 22q11DS, the IQ, and specifically its decline, is one of the most reliable predictors of subsequent psychotic onset (Kates et al., 2015; Vorstman et al., 2015). Indeed, results of three longitudinal studies examining the period of late childhood and adolescence to adulthood documented that individuals with 22q11DS developing psychosis show a

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gradual cognitive decline as they enter into adulthood (Gothelf et al., 2005; Antshel et al., 2010; Vorstman et al., 2015).

More specifically, in a prospective longitudinal cohort study, Vorstman et al. (2015) included 411 individuals with 22q11DS (mean age: 16. 1 (sd: 6.2)) with at least two IQ measurement at age 8–24 years. All patients showed a decline in IQ over time, particularly in Verbal IQ. The average total declines in cognitive abilities were 7.04 points in Full Scale IQ, 9.02 points in Verbal IQ, and 5.09 points in Performance IQ. Even more interesting, Vorstman et al., 2015 found that cognitive decline (Full scale IQ and both scales with most pronounced for Verbal IQ) was greater in individuals with 22q11DS who develop a psychotic disorder, and this decline appears to start as early as age 11 years. Overall, based on Vorstman et al., 2015, individuals with 22q11DS who develop psychotic disorder show a significant cognitive decline that is significantly steeper than the intellectual decline over childhood and adolescence observed in individuals with 22q11DS without psychosis.

Existing research has mainly considered changes in IQ as a psychosis predictor in 22q11DS, but very little research has considered other neuropsychological domains as possible predictors. In the latter context, Schneider et al. (2014b) carried out a longitudinal study (3 years between two time points) on the associations between neuropsychological profile and psychotic symptoms in a group of 56 adults with 22q11DS. The results showed that, in several neuropsychological domains (full-scale IQ, processing speed, and verbal memory), individuals with 22q11DS and psychotic symptoms were significantly more impaired than those without psychotic symptoms. However, the study by Schneider et al. (2014b) included some adults with 22q11DS who showed psychiatric disorders in comorbidity. As the authors underlined, this may have increased the prevalence of psychiatric disorders in a group of 56 adults with 22q11DS and, since the follow-up started in adulthood, the conclusions must not be considered definitive. More recently Antshel et al. (2017) examined the extent to which the developmental trajectories of cognitive abilities, academic abilities, executive functioning, attention, working memory, and emotion recognition can be predictive of psychosis in young adults with 22q11DS. Eighty-two children and adolescents with 22q11DS were assessed for psychiatric disorders and neuropsychological functioning at 4 time points, with approximately 3 years between time points. Results showed that visual and auditory working memory abilities and academic abilities improved at a slower rate for individuals with 22q11.DS than those without psychosis. More interestingly, perseverative error scores in the Wisconsin Card Sorting Test and thus, cognitive flexibility, were robust predictors of prodromal/overt psychotic symptoms in adulthood. Indeed, individuals with 22q11DS who developed prodromal/overt psychotic symptoms continued to demonstrate deficits in cognitive flexibility and improved less appreciably than individuals with 22q11DS who did not show prodromal/overt psychotic symptoms. However, the study by Antshel et al. (2017) has the limitation that longitudinal assessments were conducted every 3 years, and the possibility should be considered that changes may have occurred earlier and that developmental progression of psychotic symptoms was not detected. In addition, medication history was not controlled for. Medication may have reduced some psychotic symptoms and affected the results concerning the neuropsychological performance. Finally, the authors did not clarify the distribution of psychiatric co-morbidities amongst the patients.

The aim of the present study was to investigate, in a longitudinal perspective, the relationship between neuropsychological abilities and the onset of psychotic symptoms in a group of children, adolescents and young adults with 22q11DS. The follow-up time (12 months) in our study was shorter than that of previous studies in order to assess early changes in the clinical course of 22q11DS; furthermore, not only general cognitive abilities but also executive functioning, language (lexical comprehension) and visual-motor integration abilities were fully investigated.

In addition, the possible effects of pharmacological treatments were taken into consideration when examining the relationship between neuropsychological abilities and onset of psychotic symptoms in individuals with 22q11DS. Finally, besides psychotic symptoms, other comorbid psychiatric disorders in individuals with 22q11DS who develop psychosis and in those who do not develop psychosis were taken into account at baseline.

2. Methods

2.1. Participants

Seventy-five participants (31 females, 44 males) with a genetically confirmed 22q11DS diagnosis, aged between 6 and 27 years (14.6 ± 5.1 years) at baseline (T0), were included in the study. Participants were recruited from the Child and Adolescent Neuropsychiatry Unit and the Clinical Genetic Unit of the Bambino Gesù Clinical and Research Hospital in Rome between 2014 and 2016.

They were identified by standard cytogenetic studies using fluorescence in situ hybridisation (FISH; O'Connor, 2008) and a probe from the commonly deleted 22q11.2 region.

Participants were assessed from 6 years of age onwards, due previous reports in which the presence of psychotic symptoms in individuals with 22q11DS was also documented in school-aged children (Debbané et al., 2006). Participants were followed-up over a mean period of 12 months.

Interval time between T0 and T1 ranged from 8 months to 16 months.

The exclusion criterion was having a psychotic disorder or positive psychotic symptoms at baseline or before the first evaluation at our service.

The study was approved by Ethics Committee of the Bambino Gesù Clinical and Research Hospital in Rome and was conducted in agreement with the Italian Association for 22q11.DS microdeletion syndrome (AIdel22) in the framework of a wider project aimed at the prevention of psychopathological disorders in patients with 22q11DS. All participants provided written informed consent and parental consent for those under 18 years of age. The 75 participants were divided into two groups based on the onset of psychosis at the one-year follow-up. Onset of psychosis was diagnosed in individuals with 22q11DS presenting a score of 6 in at least one item positive for SIPS/SOPS (see paragraph on Clinical Assessment for this instrument).

The first group of participants with 22q11DS who had developed psychosis (onset psychosis - OP) at one-year follow-up (T1) consisted of 18 participants (9 females, 9 males); the second group who had not developed psychosis (without onset psychosis - WOP) consisted of 57 participants (20 females, 37 males).

The groups with OP and WOP differed significantly in terms of chronological age (OP: 18.06 ± 5.1 years; WOP: 13.5 ± 4.6 years; $p = 0.0016$ Mann-Whitney).

2.2. Measures

2.2.1. Clinical assessment

The Structured Interview for Psychosis-Risk Syndromes (SIPS/SOPS; McGlashan, 2001) was administered to all participants at T0 and T1 by a trained psychiatrist during the structured psychiatric interview. The SIPS scales include a total of 19 symptom constructs (five positive, six negative, four disorganized and four general symptoms) that are evaluated based on the presence, duration and severity of specific experiences and behavior. Each item is rated on a scale of 0 (symptom absent) to 6 (extreme or psychotic symptom intensity).

The SIPS/SOPS contains diagnostic criteria for three 'psychosis risk syndromes': attenuated psychotic symptoms (APS), brief limited intermittent symptoms (BLIPS), schizotypal personality disorder (according to the diagnostic criteria of the DSM-IV) and psychosis (score equal to 6 in any of the five positive items).