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The importance of understanding cognitive trajectories: the case of 22q11.2 deletion syndrome

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Abstract

Purpose of review—22q11.2 deletion syndrome (DS) (velocardiofacial syndrome or DiGeorge syndrome) is the most common known contiguous gene deletion syndrome and is associated with neurodevelopmental problems and diverse neuropsychiatric disorders across the life span. In this review, we discuss the wide variability in intelligence, the developmental phenotypic transitions regarding cognitive development (intelligence) from preschool to adolescence, and the importance of understanding these cognitive trajectories in 22q11.2 DS for care/management and research.

Recent findings—Longitudinal data on the cognitive development of children and adolescents with 22q11.2 DS reveal divergent cognitive trajectories. A decline in verbal IQ precedes the onset of psychosis in 22q11.2 DS.

Summary—Understanding these cognitive trajectories is important since it can guide clinicians to develop adequate support, tailored remediation, and psychiatric care and individualized follow-up.

Keywords

22q11.2 deletion syndrome; variability in cognitive abilities; divergent cognitive trajectories

INTRODUCTION

Chromosome 22q11.2 deletion syndrome (22q11.2DS), a neurogenetic condition, is the most common microdeletion syndrome affecting 1 in 2,000–4,000 live births [1–4] and involving haploinsufficiency of ~50 genes resulting in a multisystem disorder. Detection is typically achieved (after diagnosis of one of the major features of the syndrome) by fluorescent in situ hybridization or via chromosomal microarray, or by prenatal testing. Phenotypic expression is highly variable and ranges from severe life-threatening conditions to only a few associated features. Most common medical problems include congenital heart

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Conflicts of interest

None

disease (in particular conotruncal anomalies), palatal abnormalities (most frequently velopharyngeal incompetence (VPI)), immunodeficiency, hypocalcemia due to hypoparathyroidism, severe feeding/gastrointestinal differences, and subtle dysmorphic facial features [5,6]. This wide phenotypic variability and the considerable morbidity associated with 22q11.2DS poses significant challenges for both individual and population based health care management. In light of these challenges, the International 22q11.2 Consortium developed practical guidelines for managing patients with 22q11.2DS that emphasizes the multi-system nature of the condition and includes recommendations for assessment by age and at diagnosis [7,8].

Not only medical issues but also developmental/ educational and behavioral/psychiatric aspects of 22q11.2 DS are (major) concerns for most families with a child/adolescent/adult with 22q11.2 DS. Individuals with 22q11.2DS are at an increased risk for developing several psychiatric disorders; the incidence of anxiety, attention deficit, and autism spectrum disorders is increased in children with 22q11.2DS [9]. Anxiety disorders are also significantly elevated in adults [10] and schizophrenia spectrum disorders are reported in 25–30% of adults [11,12]. Given the focus of this review, we will discuss the trajectories in cognitive development from preschool to adolescence in 22q11.2 DS, and the importance of this knowledge for clinical practice and research.

COGNITIVE DEVELOPMENT IN 22Q11.2 DS

One of the first and most important questions parents and caregivers of children with 22q11.2 DS ask is what the impact will be of the 22q11.2 deletion on the global cognitive development. Knowledge on the cognitive capacities are important since it is an important part of planning intervention and re-evaluating an individualized educational plan (IEP). In this respect, it is important to keep in mind that each infant/child/adolescent/adult with 22q11.2DS is unique, and that both genes and environmental factors play essential roles in shaping brain growth and cognitive development throughout life.

Infancy and early childhood (0–4 years)

Very few studies have been published on early development in 22q11.2 DS. During infancy and toddlerhood, cardiac defects, feeding difficulties, frequent infections, gross/fine motor difficulties and expressive language delays and speech problems dominate [13,14,15]. Roizen et al. [16] reported retrospective data from 88 parents (with a child with 22q11.2 DS) about developmental milestones. Compared to sibling and community control participants, expressive language and gross motor milestones were more delayed than other areas of development. Since all studies were cross-sectional and included small samples until now, there is a need for prospective, longitudinal studies on early development in 22q11.2 DS using large samples.

From preschool to adolescence (4–18 years)

From preschool age on learning difficulties and abnormal behavior become apparent. The majority of studies have focused on the intellectual abilities in children and adolescents, and very little is known on the intellectual functioning of adults with 22q11.2 DS [17, 18]. The

level of intelligence in children and adolescents with 22q11.2 DS is highly variable and follows a normal distribution (similar to the intelligence quotient (IQ) distribution in the general population), but is shifted about 30 IQ points to the left [19, 20]. The average mean full scale IQ is in the mid-seventies (70–75) with about 55% having a borderline to normal intelligence (FSIQ > 70) and about 45% having a mild (to moderate) intellectual disability (ID) (FSIQ 55-70) and a minority experiencing moderate to severe intellectual disability [21–25]. Although the intelligence profile is highly variable, a subgroup of children with 22q11.2 DS show -during early primary school age- a discrepancy between verbal abilities and perceptual reasoning abilities, favoring the verbal domain [18, 22, 26]. This VIQ > PIQ cognitive profile however seems to change with age: by the end of primary school age (age 10 years and older) this VIQ > PIQ profile is less common observed in children with 22q11.2 DS due to the increasing problems they have within the domain of verbal comprehension and abstract verbal reasoning [27]. In a recent cross-sectional study [28] the cognitive functions –measured by a neuropsychological test battery- of a large sample of 137 subjects (ages 8–21) were compared with the performance of youth with a developmental delay and medical comorbidities and with typically developing controls. Complex cognition, specifically language and nonverbal reasoning, was most impaired in the 22q11.2 DS group.

WIDE VARIABILITY IN COGNITIVE FUNCTIONING

The neurocognitive profile is highly variable both between individuals and during the course of development: some patients function within the limits of borderline-normal intelligence while others function in the range of moderate-severe intellectual disability (ID). Current findings indicate that the genetic architecture of ID is complex, consistent with other neurodevelopmental disorders, with an important role for rare variants with large effects [29]. In the 22q11.2 DS literature, several factors have been put forward to explain this wide variability in IQ: origin of the deletion (patients with a familial deletion have been associated with lower IQ scores as compared to de novo deletions) [19,21] genetic variation within the 22q11.2 region [30, 31], gender effect (girls have higher IQ scores that boys) [32] and environmental factors such as socioeconomic status [33] and parental IQ and siblings IQ [34]. Several other possible factors that contribute to this variability in IQ have not been systematically studied yet and therefore should be the focus of future research, for example: the size of the deletion, genes within the region (*COMT*, *PRODH*, *TBX1*, *CRKL1*, etc.), the remainder of the genome/genetic background, impact of medical problems (e.g. number of hospitalizations), personality and temperament, and risk and protective factors in the environment such as the impact of therapy/remediation/anticipatory guidance, quality of life, coping strategies in the family, availability of social network support and resources…

DIVERGENT COGNITIVE TRAJECTORIES IN 22Q11.2 DS

An optimal design for studying developmental trajectories is to combine initial cross-sectional designs with longitudinal follow-up [35]. Longitudinal studies in 22q11.2 DS have found a negative correlation between age and IQ scores, particularly a decline in VIQ, suggesting that at least some of these individuals show a gradual decline in cognitive development as they grow into adulthood [30,36]. A recent longitudinal study [37] revealed -already from primary school age on- a substantial diversity in trajectories through childhood

and adolescence: a) a relative *stable IQ-trajectory*: a number of children showed adequate progress in their performance to keep up with the gradual increase of the level of cognitive requirements with age; b) a *decrease in IQ score* or *a growing into deficit trajectory* due to insufficient cognitive development leading to an increasing discrepancy with age-required norms, and c) an *absolute decline in cognitive abilities* as manifested by lower subtest raw scores for at least two subtests in a subgroup of children. A recent collaborative study by the international 22Q11 Brain Behavior Consortium (22q11.2 DS IBBC) using a large, pooled cross-sectional dataset (N= 829) including a longitudinal sub-dataset (N= 411) reported that individuals with 22q11.2 DS between 8–24 years showed an average 7-point decline in FSIQ, driven by an average 9-point decline in VIQ and an average 5.1-point decline in PIQ [38]. In the subgroup that developed psychotic symptoms, this decline was significantly steeper. Based on VIQ trajectories, those who subsequently developed a psychotic disorder and those who did not, could be distinguished already from age 11 onwards. In accordance to what is observed in general population regarding the early precursors of psychosis, a decline in verbal IQ precedes the onset of psychosis in 22q11.2 DS.

IMPLICATIONS OF IQ-VARIABILITY AND OF DIVERGENT COGNITIVE TRAJECTORIES

Given the wide IQ-variability (borderline intelligence vs. mild-moderate intellectual disability) in 22q11.2 DS, children and adolescents will follow either normal school with additional learning and educational support (starting from an IEP), or they will need special education with IEPs that are adapted to the individual needs of the child/adolescent. Secondly, given the divergent cognitive trajectories and the possible cognitive decline with age, a follow-up and re-evaluation of these abilities is necessary. Additionally, since in an important subgroup of children and adolescents a decline in IQ occurs (FSIQ, VIQ or PIQ), a continuous adaptation of the expectations and the learning environment will be necessary in order to have a good balance between the cognitive capacities of the child/adolescent and the demands of the environment [39]. In this way, anticipatory guidance and tailored remediation/intervention can be implemented at home and in school, and unnecessary stress can be prevented.

From a research perspective, given the early cognitive decline in 22q11.2DS, this microdeletion syndrome/CNV is an interesting model to investigate possible genes, genetic mechanisms and central neurotransmitter systems in the 22q11.2 region that contribute to cognitive deterioration. A nice illustration of this approach is a recent study by Evers et al. [40]. Their results suggest that a subgroup of adults with 22q11.2 DS may be affected by a neurodegenerative process affecting at least three neurotransmitter systems (serotonin, dopamine and norepinephrine), but the precise mechanism of the cognitive deterioration as seen in 22q11.2 DS, has to be elucidated.

CONCLUSION

There is a wide variability in cognitive abilities and profile in children and adolescents with 22q11.2 DS ranging from borderline intelligence to mild-moderate intellectual disability. This profile is often colored by a complex associated medical phenotype which frequently

results in multiple hospitalizations beginning at an early age. Children with a parent who also has 22q11.2DS are at greater risk for a poorer long term outcome, and these families need more intense support and follow-up throughout life [39].

Educators/remedial teachers and psychologists/ psychiatrists are important members of the multidisciplinary team of professionals who provide services to a child/adolescent and adult with 22q11.2 DS.

Recent longitudinal studies on the cognitive development of children and adolescents with 22q11.2 DS reveal substantial diversity in cognitive trajectories through childhood and adolescence: a relative stable IQ trajectory over time (trajectory of delay), a 'growing into deficit' trajectory and a trajectory of an absolute decline in IQ, in particular VIQ. This latter trajectory precedes the onset of psychosis in 22q11.2 DS. This recent knowledge is an important finding since it can guide clinicians to develop adequate support, tailored remediation, and psychiatric care and individualized follow-up.

FUTURE RESEARCH

More longitudinal studies using large samples with longer time frames and several follow-ups (time-points) throughout the lifespan (from infancy into adulthood) will be needed. The 22q11.2 International Brain Behavior Consortium (22q11.2 IBBC) offers a unique opportunity to establish and reach these goals. In addition, further research should use more appropriate such as controls matched for age and IQ, and –if possible- medical comorbidities such as type of congenital heart defects, immunological and endocrinological profiles, neurological associations etc….

Finally, future studies should also pay attention to how individual characteristics such as medical factors, neuropsychological factors (e.g. executive functions, working memory), psychiatric comorbidities, family (parenting style, coping styles) and environmental factors (risk and protective factors, therapy/intervention, adaptive learning environment,….) might affect these trajectory patterns. Understanding what drives these diverse developmental outcomes and changes will be crucial. It is our hope that more knowledge of the developmental trajectories in 22q11.2 DS, will help to identify the profiles of clinical needs and may guide intervention and treatment decisions with the ultimate goal to optimize quality of life for all individuals.

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KEYPOINTS OF THE PAPER

- There is a wide variability in cognitive abilities in individuals with 22q11.2 DS
- Divergent cognitive trajectories occur already from primary school age on
- A decline in VIQ precedes the onset of psychosis in 22q11.2 DS
- More knowledge of the developmental trajectories in 22q11.2 DS will help to identify the profiles of clinical needs and may guide intervention and treatment decisions