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Cognitive, Behavioural, and Psychiatric Manifestations of 22q11.2 Deletion Syndrome.

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Introduction:

22q11.2 deletion syndrome (also commonly known as DiGeorge, or velocardiofacial syndrome) is the most common known chromosomal deletion, occurring in approximately 1 in 4000 live births. The condition is characterized by extremely variable clinical presentation. Due to this variability, there are no diagnostic criteria which must be met in order to clinically diagnose the condition. Instead, diagnosis of 22q11.2 deletion syndrome is based on molecular genetic testing, typically by array comparative genomic hybridization (aCGH) or fluorescent in situ hybridization (FISH). Therefore, some individuals may remain undiagnosed, and the true incidence of the condition may be higher than has been noted in the literature.

Despite there being no consistent physical findings, there are common clinical features which can provide clues to a diagnosis of 22q11.2 deletion syndrome. Children with the condition commonly have conotruncal cardiac defects (seen in 74% of individuals), renal anomalies (30%), and palate abnormalities (69%). Velopharyngeal insufficiency (VPI) due to submucosal cleft palate is the most common palate finding, but overt cleft lip and/or palate may also be present (Zori et al. 1998; McDonald-McGinn et al. 1999). Feeding difficulties due to hypotonia are also a frequent finding in infancy. Characteristic facial features are present in most individuals with the condition, but are usually subtle (Guyot et al. 2001). Children with 22q11.2 deletion syndrome often exhibit immunodeficiency due to thymic hypoplasia. This impaired T-cell production tends to be most severe in newborns and improves over time. Hypoparathyroidism is also frequent in newborns, but tends to subside in adulthood. However, hypocalcemia is a common complication in the adult period.

Children with 22q11.2 deletion syndrome are usually developmentally delayed. Learning difficulties are present in nearly all individuals with the condition, although severe intellectual disability is rare. Autism spectrum and attention deficit disorders have also been noted in childhood. By adulthood, up to 1/3 of individuals with 22q11.2 deletion syndrome develop schizophrenia or schizoaffective disorder, and approximately 60% of adults with the deletion have a diagnosed psychiatric disorder.

22q11.2 deletion syndrome is an autosomal dominant condition, meaning that only one copy of the deletion is necessary for the condition to be expressed. It is estimated that 93% of 22q11.2 deletions are new in a child, or *de novo*, and that 7% are inherited from a parent. The 22q11.2 deletion is equally likely to occur during spermatogenesis or oogenesis. The majority of deletions are 3 megabases (MB) in size, but smaller deletions have been reported, most notably a 1.5 MB deletion in approximately 8% of individuals. The size of deletion is not correlated with the severity of the phenotype, suggesting that this 1.5 MB region is largely responsible for the clinical features associated with the syndrome.

Duplications of the 3 MB 22q11.2 segment also occur frequently, but the phenotype associated with such duplications is much less well-defined. A number of individuals are noted to have conotruncal cardiac defects or VPI, suggesting that gene dosage effects may play a role in this region (Phillip and Basset 2011).

Cognitive Profile:

Most children with 22q11.2 deletion syndrome are delayed in their achievement of developmental milestones, beginning in early infancy. Mild to significant language delays are present in the majority of children, and two-thirds of children do not exhibit expressive language by two years of age (Gerdes et al. 2001). Early gross motor delay is also common, and is most likely related to hypotonia (Gerdes et al. 2001).
Learning difficulties are present in nearly all individuals with 22q11.2 deletion syndrome. These difficulties may be identified in children from preschool through to high school and may have an impact on adult functioning (Philip and Basset 2011). The majority of school-aged children with 22q11.2 deletion syndrome are noted to have 'borderline intellectual functioning', with an IQ of 70-84. (Shprintzen 2000, Drew et al. 2011, Philip and Bassett 2011). A smaller minority of children exhibit mild intellectual disability, with an IQ of 55-70, and less frequently, intelligence is measured in the low average range (IQ>85) (Drew et al. 2011). Severe intellectual disability is rare in individuals with the condition.
In general, children with 22q11.2 deletion syndrome have significantly higher verbal IQs than performance IQs, suggesting a nonverbal learning disability in children with the condition (Swillen et al. 1999). Arithmetic tends to be a particular problem area for individuals with 22q11.2 deletion syndrome, but reading, spelling, and verbal memory scores are relatively high (Drew et al. 2011). Interestingly, the nonverbal learning difficulties observed in 22q11.2 deletion syndrome are similar to cognitive profiles in other neurogenetic disorders such as Fragile X, Williams, and Turner syndromes (Karayiorgou 2010).
Several studies suggest that attention deficits could be largely responsible for the psychoeducational profile seen in 22q11.2 deletion syndrome (Drew et al. 2011.) Attention impairment can lead to difficulties identifying and interpreting salient spatial and temporal information. Children with a 22q11.2 deletion have demonstrated struggles with counting ability, 'magnitude comparison' and 'time duration comparison', all of which require sustained attention. These difficulties together are suggested to account for the broader deficits in numeric and visuospatial ability which are seen in children with the condition.

Autism Spectrum and Attention Deficit/Hyperactivity Disorders in Childhood:

The prevalence of autism spectrum disorders in children with a 22q11.2 deletion is not well-defined. In a sample of 100 children and adults with 22q11.2 deletion syndrome, 23 were found to have autism spectrum disorders, whereas 5 were identified to have autistic disorder (Niklasson et al., 2009). This study also diagnosed 30 individuals with ADHD. Nonetheless, these are commonly diagnosed problems, particularly in school-aged children, and whether they are enriched in individuals with 22q11.2 deletion syndrome has not been definitively determined. An ascertainment bias may be present in individuals with the syndrome as they are more likely to come to clinical attention. Moreover, it has been suggested that standard assessment methods for these disorders are not accommodating for individuals with neurodevelopmental disabilities. Thus, using these methods, cognitive features associated with 22q11.2 deletion syndrome may be misdiagnosed as ASD or ADHD despite being part of a distinct behavioural phenotype (Niklasson et al. 2009). Behaviours common in children with 22q11.2 deletion syndrome include difficulty socializing, dependence on a caregiver, impulsivity, temper outburst, perseverative speech, and repetitive behaviours (Philip and Bassett 2011).

Psychiatric Disorders in Adulthood:

More research is required to refine the behavioural-cognitive phenotype associated with 22q11.2 deletion syndrome in adulthood. One study (Fung et al. 2010), found that 60% of adults with 22q11.2 deletion syndrome had at least one psychiatric disorder. In this study, 40 adults with the condition were recruited from a cardiac clinic in order to minimize bias of ascertainment. In this sample, nine (22.5%) subjects had schizophrenia or schizoaffective disorder. Five (12.5%) patients had generalized anxiety disorder, which is higher than prevalence estimates from the general population. Major depression (17.5%), obsessive compulsive disorder (5.0%), social phobia (5.0%), attention deficit hyperactivity disorder (7.5%), and substance abuse issues (12.5%) were noted in this population. However, prevalence estimates were not significantly different from those in the general population. Initial data (Booji et al. 2010, Zaleski et al. 2009) suggest that early-onset Parkinson's disease may be a feature of the syndrome, but more comprehensive studies are required to demonstrate an association.

Susceptibility to schizophrenia:

Up to 1/3 of individuals with 22q11.2 deletion syndrome develop schizophrenia in late adolescence or early adulthood, and it is estimated that 1-2% of individuals with sporadic schizophrenia have a 22q11.2 deletion. Therefore, a 22q11.2 deletion is one of the most powerful identified risk factors for development of a psychotic disorder. Individuals with 22q11.2 deletion syndrome develop schizophrenia at a similar age and exhibit similar clinical findings as those who do not possess the deletion (Karayiorgou et al. 2010). In general, predictive prodromal symptoms are similar to those seen prior to idiopathic schizophrenia – attention deficit, mood and anxiety disorders, and impaired social interactions (Karayiorgou et al. 2010). Children with more severe intellectual disability or physical features associated with 22q11.2 deletion syndrome do not have a greater risk of developing schizophrenia later in life.

Neuroanatomical Changes:

Most genes affected by the 22q11.2 deletion are expressed in the brain (Karayiorgou 2010). 22q11.2 deletion syndrome is suggested to be a neurodevelopmental disorder, since brain anatomy is typically normal in infancy, but neuroanatomical changes become progressively more apparent with age. In children, ventriculomegaly is commonly noted with a reduction in total brain volume, which is greater in the anterior versus posterior region, and white matter tends to be more severely affected (Karayiorgou et al. 2010; Drew et al. 2011). White matter changes characteristic of 22q11.2 deletion syndrome are hypothesized to be causative of the learning difficulties associated with the condition (Woodin et al. 2001) but more research is required to link specific neuroanatomical changes with behaviour (Karayiorgou et al. 2010).
In adults with schizophrenia, brain volume is further reduced relative to healthy controls and other individuals with 22q11.2 deletion syndrome who are not affected by a psychotic disorder (Drew et al. 2011). Further, enlarged lateral ventricles are a common finding in individuals with 22q11.2 deletion syndrome, and are also frequently seen in individuals with idiopathic schizophrenia

Conclusion:

22q11.2 deletion syndrome is a complex, multi-system disorder. Children with the condition often have special social, cognitive, and physical needs. Therefore, families of children with 22q11.2 deletion syndrome may face challenges when trying to promote their child's healthy development. Support resources are available to assist with this process.

Support Resources:

- International 22q11.2 Deletion Syndrome Foundation, Inc.
  P.O. Box 2269
  Cinnaminson NJ 08077
  Phone: 877-739-1849 (toll-free)
  Email: info@22q.org
  www.22q.org

- International DiGeorge/VCF Support Network
  c/o Family Voices of New York
  46 1/2 Clinton Avenue
  Cortland NY 13045
  Phone: 607-753-1621 (day); 607-753-1250 (eve)
  Fax: 607-758-7420

- Chromosome Disorder Outreach (CDO)
  PO Box 724
  Boca Raton FL 33429-0724
  Phone: 561-395-4252 (Family Helpline)
  Email: info@chromodisorder.org
  www.chromodisorder.org/CDO

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About the RCPU:

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20, F.S., of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate intellectual disabilities through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects.

Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of intellectual disabilities. Staff members are available for consultation and for educational programs for health professionals and for the community at large.

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