Commentary

The genetic basis of attention deficit hyperactivity disorder (ADHD) has not yet been completely unraveled. There is an increasing focus on rare genetic variant hypothesis of ADHD. In this background, DiGeorge syndrome, velocardiofacial syndrome, Williams-Beuren microdeletion syndrome, and chromosome 15 duplication syndromes have been some of the chromosomal abnormalities described.^[1,2] A genome-wide association study has reported that rare copy number variants as well as duplications have been consistently identified at 15q13.3 with odds ratio of 2.2.[1] The duplicated region has been found to contain gene CHRNA 7 which is found to regulate dopamine release and thereby identified as a potential genetic marker for ADHD.[3] The article titled, "Chromosome 15 duplication and ADHD: A case report" published in this issue illustrates the issues pertinent to management of chromosome 15 duplication and ADHD.[4]

Chromosome 15 duplication has been largely studied in the q11-q13 region and also in q21.3. The phenotypic manifestations of chromosome 15 duplication have been found to be variable, expressed as normal, nonspecific developmental delay to speech, motor and global developmental delay, agenesis of the corpus callosum, cerebellar heterotopia, seizure disorder, dysmorphic facies, strabismus, short stature, parasomnias, autism spectrum disorder (ASD), ADHD, specific learning disability (SLD), depression, behavioral problems such as aggression, Prader-Willi syndrome, and Angelman syndrome. [5,6] The type of chromosomal duplication has been broadly divided into idic type (having extra copy/copies of chromosome leading to supernumerary chromosomes) and interstitial type (extra chromosome copy incorporated within chromosome 15).[7]

Participants with maternally derived duplication, which is more common, predominantly exhibited symptoms of ASD. Children with paternally derived duplication were found to present with behavioral problems or delay in speech. There is preliminary, yet inconclusive evidence that paternal duplication might be specific to ADHD.^[8]

WHEN TO SUSPECT CHROMOSOMAL DUPLICATION 15 IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER

Patients with constellation of symptoms and signs such as intellectual disability (ID), features of ASD, seizures, history of global developmental delay, delay in motor or language milestones, hypotonia, dysmorphic facies such as epicanthal folds, downward slant of palpebral fissure, and upturned nose need to be evaluated for chromosome 15 duplication.^[7] In the article, chromosomal abnormality was suspected due to symptoms such as hypotonia, weak cry, dysmorphic facies, and difficulty in feeding.

ASSESSMENT

Patients in whom chromosome 15 duplication is suspected a careful history taking including family history and thorough general and systematic examination must be carried out. Structured assessment must be done for ruling out psychiatric comorbidity such as ASD, conduct disorder, and SLD. Formal assessment for testing intelligence quotient should be done in cases in whom ID is suspected. Active efforts must be put for evaluating for disorders of sleep such as parasomnias. Electroencephalogram should be done to look for epileptiform discharges. Neuroimaging needs to carried out to assess for structural brain abnormality.

TREATMENT CHALLENGES

Multimodal management involving pharmacotherapy, speech therapy, occupational therapy, physiotherapy, and behavioral therapy is advised for the management neuropsychiatric manifestations. **Psychotropic** medication is advised to treat the behavioral problems. No systematic literature could be found about choice of psychotropics in this condition. Case reports suggest that methylphenidate could be beneficial for the management of ADHD and risperidone for the management of ASD and aggression. Selective serotonin reuptake inhibitors were found to increase aggression. Bupropion could be avoided considering reported worsening of aggression as well as seizure-inducing potential.[6] It is also important to carefully monitor for adverse effects in the background of increased susceptibility to adverse effects. The authors of the article have reported the effectiveness of methylphenidate in improving symptoms of ADHD though initial restlessness was reported. Further, they have emphasized the need for starting low dose and preferring longer-acting preparation.[4]

Periodic neurodevelopmental assessment, as well as monitoring for seizures, must be carried out. The parents must be psychoeducated about the nature, course of illness, associated comorbidity, avoiding sleep deprivation, maintaining sleep hygiene, need for regular monitoring, and compliance to treatment.^[7]

Genetic counseling may be advised for parents with a child with chromosome 15 duplication. The chance of sibling having chromosomal duplication is found to be about 50% in cases of maternal interstitial duplication. However, the risk is lower in cases of maternal idic duplication.^[7]

Hence, cases with ADHD with chromosome 15 duplication offer several management challenges. The trainees in psychiatry and pediatrics alike must be sensitized about the need for screening for chromosomal abnormalities in children with ADHD presenting with atypical symptoms in clinical practice. The chromosome 15 duplication offers new insights into the neurobiological understanding of ADHD. Furthermore, the overlap of genetic abnormalities as well as frequent co-occurrence of ADHD, ASD, SLD, and conduct disorder clinically needs to be further evaluated for pleiotropic inheritance.

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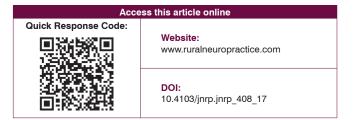
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How to cite this article: Kuppili PP. Commentary. J Neurosci Rural Pract 2017;8:662-3.