Case Report

Chromosome 15 Duplication and Attention-Deficit Hyperactivity Disorder

Sundar Gnanavel

Children and Adolescent Mental Health Services, Northumberland, Tyne and Wear NHS foundation trust, UK

ABSTRACT

Chromosome 15 duplication has been associated with a number of psychiatric illnesses including psychosis and autism. However, literature on association with attention-deficit hyperactivity disorder (ADHD) is scant. This case report describes a patient with chromosome 15 duplication diagnosed with ADHD in our neurodevelopmental clinic. The possible biological underpinnings are discussed along with possible challenges in diagnosis and management. The need for better understanding ADHD as a behavioral phenotype in such cases along with need for tailored management strategies is emphasized.

KEYWORDS: Attention-deficit hyperactivity disorder; chromosome 15 duplication, genetics

INTRODUCTION

Deletions and duplications in chromosome 15 have previously been implicated in several psychiatric disorders including neurodevelopmental disorders and severe mental illnesses such as schizophrenia as well as physical illnesses such as epilepsy.^[1,2] The duplicated region contains a putative candidate gene for attention-deficit hyperactivity disorder, CHRNA7, which encodes the $\alpha 7$ subunit of the neuronal nicotinic acetylcholine receptor, an ion channel involved in calcium signaling in the brain. The $\alpha 7$ nicotinic acetylcholine receptor also participates in a neural pathway pertinent to ADHD by mediating the release of neurotransmitter dopamine.^[3] Dopamine dysregulation is implicated in ADHD, and $\alpha 7$ receptor agonists have shown some efficacy in the treatment of ADHD in experimental studies.^[4] There is some evidence to indicate that this gene is a potential candidate for parent-of-origin and gene-environment interaction studies in ADHD.^[5] However, while there are case reports of patients with autism and other psychiatric disorders with duplication of chromosome 15, literature on association of ADHD with the same is scarce. In this case report, we describe a case of chromosome 15 duplication with ADHD along with discussions on management and need for more customized evidence-based pharmacological therapy in such cases.

CASE REPORT

A 15-year-old boy was referred to the neurodevelopmental clinic of our child and adolescent mental health services for a diagnostic assessment. He was assessed in the presence of his parents.

The primary concerns included difficulty in sustaining his concentration, organizing sequential tasks, completing tasks on schedule, being forgetful often, and easily distractible shifting to different tasks in quick succession. He was reported to be restless and fidgety in multiple settings including at school and home, with his difficulty being seated at his desk in classroom. He also encountered difficulties in waiting for his turn or in a queue and engaging in group activities. His symptoms were associated with significant impairment in his functioning at home and school. The rating scales from his parents as well as teachers (Conner's questionnaires) in addition to the school observation and occupational therapy group assessment reports supported the above findings. There were no pointers toward autistic traits or intellectual difficulties. Furthermore, there was no history suggestive of anxiety or mood symptoms.

Address for correspondence: Dr. Sundar Gnanavel, 35, St Anns Close, Newcastle Upon Tyne NE1 2QP, UK. E-mail: sundar221103@yahoo.com

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He lives with his parents and two biological siblings. There is a family history of ADHD in one of his paternal cousin brothers (who has not been genetically tested). His antenatal history was uneventful. However, there were reported difficulties with sucking, feeding, and a low-pitched crying. He also appeared floppy though these difficulties eventually self-resolved. There were also delays in gross motor and language milestones, which he was eventually caught up with. There are no active physical health concerns currently. There is no history of seizure episodes.

During the assessment, he came across as a lively and boisterous boy who was warm and friendly. He made appropriate eye contact and expressed a range of facial emotions. However, he was constantly distracted by different environmental stimuli. He could not be engaged in a conversation on any specific topic beyond a few minutes since he kept losing thread of the conversation. There were no autistic traits elicited in history or during the interview.

On review of previous investigations, it was noted that genetic analysis fluorescent *in situ* hybridization technique was carried out, and it revealed chromosome 15 duplication (tested for the following constellation of clinical features: hypotonia, weak cry, and difficulties with sucking and feeding). No formal IQ testing has been carried out since he has been above average with his school lessons despite his attentional and behavioral difficulties, and there are no other pointers suggestive of intellectual or learning difficulties. Downslanting palpebral fissures were noted during the general examination. His height was measured to be 162.5 cm (14th centile) and he weighed 45.3 kg (8th centile) on the day of diagnostic assessment. His cardiovascular parameters (blood pressure and pulse rate) were within normal limits.

A diagnosis of ADHD and combined subtype was made based on the history, mental state examination, and other reports. His carers were psychoeducated regarding the disorder and different management options (pharmacological and nonpharmacological). Conners' rating scale (parental version) was administered at baseline (t-score >70).^[6] The side effects of stimulant medication were discussed along with the potential benefits emphasizing that individuals with chromosomal mutations may tolerate stimulant medication differently. Taking this into account, it was decided to initiate him on 5 mg of methylphenidate, to be titrated upward gradually. It was also explained that we would be monitoring his growth at every visit (height and weight) along with his cardiovascular parameters (blood pressure and pulse rate). They were also provided self-help

material on ADHD, and the parents were referred for parenting classes after their consent.

He was reviewed subsequently on multiple occasions. There was some initial increase in restlessness and agitation over the initial week. Fortunately, he later tolerated the medication reasonably well and no significant side effects were reported. The dose of methylphenidate was very gradually increased to 30 mg daily, and thereafter, he was shifted to longer acting preparation of methylphenidate, concerta-extended release 27 mg once daily to simplify the drug regimen. At a subsequent review 4 months from the index visit, Conners' rating scale (parental version) was readministered (t-score <60) demonstrating a significant reduction in symptomatology.

DISCUSSION

This case report highlights the need for research on genetic susceptibility markers for ADHD, identification of any specific behavioral phenotypes of ADHD secondary to genetic causes, and developing targeted medication interventions in these unique cases (e.g., drugs acting on nicotinic receptors in this case). At the moment, "start low and go slow" pertaining to dosage of medication, being more vigilant for adverse effects, and being more mindful of comorbid physical health concerns would be the prudent strategies for these rare subset of patients with ADHD and genetic mutations.

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Conflicts of interest

There are no conflicts of interest.

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