Case Report

Chromosome 1p31.1 Deletion Syndrome: Limited Expression

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Abstract

Chromosomal microdeletion syndromes usually present with neurological abnormalities, developmental delays, and various systemic abnormalities. 1p31 microdeletion syndrome is one of the novel microdeletion syndromes that usually presents with developmental delay, intellectual disability, various craniofacial abnormalities, and other systemic abnormalities in a proportion of cases. NEGR1 and NFIA are few of the genes present in this locus responsible for these symptoms. However, none of the reported cases had only isolated intellectual disability. Here, we are reporting a case of 1p31 microdeletion syndrome with isolated moderate intellectual disability and hyperactivity in an 11-year-old boy. It is essential for clinicians to be aware of such an atypical presentation of 1p31.1 microdeletion syndrome, to maintain reasonable clinical suspicion in cases with unexplained intellectual disability.

Keywords: Facial dysmorphism, hyperactivity, inattention, intellectual disability, neurodevelopmental disorder

Introduction

Chromosomal microdeletion syndromes are usually too small to be detected by karyotype, but the deleted region often encompasses many essential genes. Although most of them are de novo in origin but tend to involve a few specific chromosomal regions.[1] This is due to the homologous recombination of flanking gene clusters with low copy repeats (duplicons), which are prone to duplication, deletion, and inversion. Commonly they present with a variable combination of neurodevelopmental problems and systemic abnormalities.[1] Only a few classical microdeletion syndromes like Angelman, Prader–Willi, Williams–Beuren, Smith–Magenis, and DiGeorge syndromes have recognizable clinical phenotypic features and can be identified by fluorescent *in situ* hybridization.[2] Currently, with the availability of high-resolution chromosomal microarray and whole-exome sequencing, many novel microdeletions and other neurogenetic syndromes are discovered in recent years.[3-5] Only a few anecdotal case reports of this rare microdeletion syndrome are available in the literature and most of them presented with facial dysmorphism and various systemic abnormalities, associated with developmental delay and often neuroimaging abnormalities like ventriculomegaly and corpus callosum hypoplasia.[6] Unlike to reported cases, we wish to describe an atypical case of 1p31 microdeletion syndrome, for the first time from the Indian subcontinent, who presented with isolated intellectual disability.

Case Summary

An 11-year-old boy presented with poor generalized understanding, with inattention and hyperactivity. The child was born to a nonconsanguineous couple by normal vaginal delivery at 39 weeks of gestation, without any perinatal adverse event. He had a global developmental delay, with independent walking achieved at 3 years of age. Language milestones were comparatively more delayed, and the child spoke the first meaningful word at 5 years of age. At 11 years of age, the child was able to speak small sentences only. He was requiring some assistance for performing activities of daily living and was attending special education classes for children with intellectual disabilities.

On physical examination, his weight, height, and head circumference were within normal limits. He did not have any obvious dysmorphic facial features or other abnormalities on physical examination [Figure 1]. Full scale (verbal and performance) intelligence quotient (IQ) on Malin's Intelligence Scale for Indian Children was 49 (moderate intellectual disability). Although the child did not meet the Diagnostic and Statistical Manual-V (DSM-V) criteria for attention deficit hyperactivity disorder (ADHD), he had hyperactivity and attention problems in the clinical range in Child Behavior Checklist. Skeletal X-rays [Figure 1], ultrasonography of the abdomen, echocardiogram, and magnetic resonance imaging of the brain was unremarkable [Figure 2]. Karyotyping

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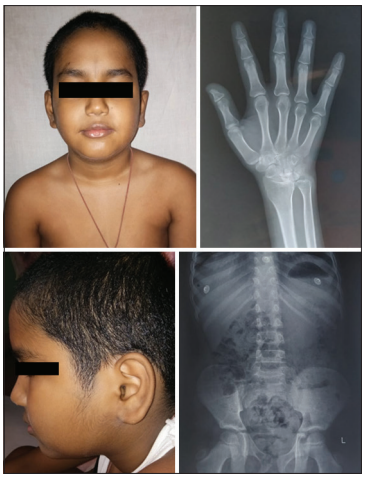

Figure 1: Facial photographs and skeletal X-rays of the child with 1p31 microdeletion syndrome. Facial photographs (frontal and lateral view), X-ray wrist (antero-posterior view) and spine with the pelvis (antero-posterior view) did not reveal any abnormalities

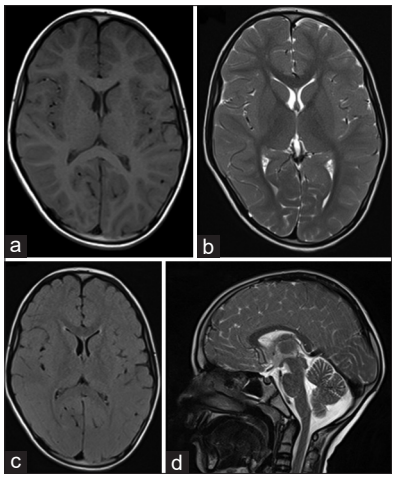

Figure 2: Magnetic resonance imaging of the brain (axial sections: -A-T1W, B-T2W, C- FLAIR and sagittal sections:- D-T2W) of the child with 1p31 microdeletion syndrome was essentially normal

revealed normal 46, XY karyotype, and work up for fragile-X syndrome was negative. Chromosomal microarray analysis (CMA) revealed a partial deletion (5.99 Mb in size) of the chromosomal 1p31.1 was found with coordinates: chr1: 71.541.998–77.529.328 [copy number variation (CNV) ratio 0.51]. No other microarray abnormalities were noted. Parental testing was unremarkable, suggesting this variant in index case to be of de novo origin. The CNV detected was considered pathogenic, as microdeletion of this region at location Chr1p31.1 has previously been reported in patients affected with intellectual disability and severe language impairment, thereby establishing the genotype-phenotype correlation. The parents were provided with appropriate genetic counseling, along with rehabilitation advice for the affected child.

Discussion

Interstitial microdeletion at 1p31.1 site has been described by few authors previously to cause intellectual disability, but in almost all cases associated with other dysmorphic features, cardiac or skeletal anomalies, depending on the size of microdeletion and characteristics of encompassing genes. Genovese *et al*. in 2015 described two siblings with intellectual disability, who harbored a partial deletion of chromosome 1p31.1 including only the neuronal growth regulator 1 (NEGR 1) gene. But they also had microcephaly, hypertonia, micrognathia, broad nasal tip, a tendency for an open mouth, short neck, fifth finger clinodactyly, and brachydactyly. Apart from behavioral abnormalities like hyperactivity and inattention, they also had aortic root dilatation, hypermobility of joints, and scoliosis.[3] The NEGR1 gene has been found to affect neuronal growth, proliferation, and differentiation. It is strongly expressed in the cerebral cortex, hippocampus, olfactory bulb, and hypothalamus. The NEGR1 gene has also been proposed to play a role in obesity or bodyweight control.[7]

The second report of 1p31.1 microdeletion with isolated NEGR1 gene disruption in a 14-year-old girl and a 5-month-old girl was recently published by Tassano *et al*.[8] Apart from developmental delay and intellectual disability; the first case also had bipolar disorder and ischemic stroke leading to left periventricular gliosis and right hemiparesis, along with the family history of these disorders.[8] The second case also had central hypotonia, horseshoe kidney, one episode of an apparent life-threatening event with cyanosis, and sucking difficulty. Surprisingly, a recently completed genome-wide association study by Liu *et al*. identified a functional human-unique 351 base pair Alu insertion polymorphism in the 1p31.1 loci, associated with major depressive disorder.[9]

Mircher *et al*. have described a similar phenotype in 10 children harboring interstitial deletions of the 1p31 chromosomal region.[10] Apart from intellectual disability and hypertonia, these children also possessed micrognathia, fifth finger clinodactyly, large space between first and second toes, and broad nasal tip. In 2017, Thakur *et al*. reported an infant with congenital hypopituitarism, associated with septo-optic dysplasia with an absent anterior pituitary and an ectopic posterior pituitary gland, caused by a de novo 8.04 Mb interstitial deletion involving chromosome 1p31.1–1p31.3. The deleted region included several genes involved in pituitary development, including LEPR and JAK1, which were not involved in the CNV reported in our case.[11]

Rivera-Pedroza *et al*. in 2017, described another female with a large 1p31.1p31.3 deletions of 18.6 Mb size, who had a cloverleaf skull, hypotelorism, and severe exophthalmos with the absence of eyelids, ectopia lentis, sclerocornea, cleft palate, low-set ears, and cutis laxa, obstructive hydrocephalus, small posterior cranial fossa, intracerebral hemorrhage, bilateral renal hypoplasia. She also had other previously described clinical features of 1p31.1 microdeletion syndrome including developmental delay, seizures, round face with a prominent nose, micro/retrognathia, half-opened mouth, short neck, hand/

foot malformations, hernia, congenital heart malformations, and abnormal external genitalia.[12] However, an isolated neurodevelopmental phenotype with intellectual disability and behavioral abnormalities in our case denotes a unique presentation of this 1p31.1 microdeletion syndrome.

Another gene located in 1p31 loci, whose disruptions have been associated with an intellectual disability is the NFIA gene, reported in eight cases by different investigators till now. Koehler *et al*. reported an infant female with novel 1p31.3p32.2 deletion involving the NFIA gene, with macrocephaly, hypoplasia of corpus callosum, ventriculomegaly, and facial dysmorphism.[13] Rao *et al*. have recently reported an 8-year-old girl with the first case of intragenic deletion of the NFIA gene at 1p31 loci, who presented with the abovementioned features, along with macroscopic hemoglobinuria and metopic synostosis.[6]

Conclusions

1p31 microdeletion syndrome should be clinically suspected in children with developmental delay and intellectual disability. Although the presence of various craniofacial abnormalities increases suspicion of 1p31 microdeletion syndrome, rarely intragenic deletions involving NEGR1 and NFIA can present with isolated neurodevelopmental delay phenotype.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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