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MEDICINE

A RARE CASE OF CHROMOSOME 16P11.2-P12.2 MICRODUPLICATION SYNDROME

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Background: genetic syndrome, microduplication of chromosome 16p11.2-p12.2 characterized by treatment-refractory epilepsy accompanied by global developmental regression, facial dysmorphia, hyperactivity, multiple allergies.

Key words: microduplication syndrome, chromosome 16p11.2-p12.2, epileptic and developmental encephalopathy, autistic spectrum disorder, polymorphic seizures

CASE PRESENTATION

We report a novel of a heterozygous duplication of the 16p11.2-p12.2 region, encompassing the critical region for 16p11.2-p12.2 duplication syndrome, in a Caucasian girl.

CONCLUSIONS

Our report further confirms that mutation of of the 16p11.2-p12.2 chromosome results in developmental and epileptic encephalopathy characterized by treatment-refractory epilepsy and autistic spectrum disorder.

BACKGROUND

Recent discoveries highlight recurrent copy number variations in chromosome 16p. Specifically, rearrangements in 16p11.2 have been linked to autism, intellectual disability, epilepsy, and other neurodevelopmental conditions, physical anomalies, small head size, shorter height, and slender fingers. Less commonly these patients present irregularities in MRI/CT scans[1,2,3].

Microduplications in 16p are connected to a broad range of neurobehavioral issues, such as autism spectrum disorder, intellectual disability, attention deficit hyperactivity disorder, seizures, and schizophrenia[3-9]. Interestingly, 16p11.2 deletions and duplications respectively elevate the risks of weight abnormalities, obesity being associated with deletions and underweight with duplications[1,3,9,10].

We report a rare case of a Caucasian girl with negative family history, polymorphic epilepsy, autistic spectrum disorder, hyperkinetic disorder, language delay and facial dysmorphic features: deep-set eyes, thick supra-orbital ridge with thick eyebrows, wide and prominent nasal bridge, round face, full cheeks, wide philtrum, short stature.

We present the case of a 6-year-old girl, delivered by cesarean section at full term, with good perinatal adaptation and normal neuropsychomotor development up to 1 year of age. The girl had her first epileptic seizures at 1 year old, during sleep, with a generalized tonic-clonic appearance, followed by absences and atonic seizures. Over time, the patient displayed symptoms of the autism spectrum: hyperactivity, stereotypies, mixed language delay, echolalia. Notably, the patient has multiple allergies. Extended sleep electroencephalographic evaluation

revealed generalized spike and polyspike discharges suggestive of absences and complex spike-wave discharges on the left occipital leads. The 3T MRI brain imaging was normal. The girl was treated with carbamazepine and levetiracetam, clobazam, but there was no improvement in her health. Subsequently, the antiepileptic treatment was changed to a combined regimen of valproic acid and ethosuximide, adjusted to the child's weight, and the evolution was favorable. With the combined treatment regimen of valproic acid and ethosuximide, the child showed improved consciousness, behavior, and cognitive acquisitions after a period of 6 months. To improve autism spectrum symptoms, the child underwent cognitive-behavioral therapy and language stimulation therapy.

DISCUSSION

Due the absence of a family history of the disease, the patient's exome data was examined for rare heterozygous variants (potential de novo variants) and those that fit a recessive inheritance pattern. Exome sequencing revealed a heterozygous duplication on chromosome 16, specifically in bands 16p11.2-p12.2. This duplication spans the genomic region 16: g.21413544-29001413dup and measures approximately 7.58 Mb.

The observed duplication in our patient impacts 70 coding genes, covering the essential region associated with the known recurrent duplication responsible for the 16p11.2-p12.2 duplication syndrome (as cataloged in Decipher – CNV Syndromes/16p11.2-p12.2 microduplication syndrome).

In 2020, Lengyel and colleagues documented a case resembling ours, involving a boy who exhibited sensorineural hearing loss, scoliosis, anal and tracheal narrowing, minor motor delay, speech articulation challenges, hyperactivity, and symptoms of the autism spectrum. While his brain MRI was unremarkable, his EEG identified frontotemporal epileptic abnormalities, which responded well to valproic acid treatment[12].

In 2004, Finelli and colleagues documented another similar case involving a 25-year-old male presenting with a distinct facial appearance characterized by asymmetry, a squared profile, widened space between the eyes, broad nasal bridge and tip with a pronounced columella, short upper lip area, elongated ears, an expansive mouth with pronounced lips, and large, uneven teeth. This individual was diagnosed with autism spectrum disorder, exhibited an unsteady walk, had bilateral clubbed feet, showed limited dexterity, was hyperactive, displayed attention deficits, and experienced seizures that were managed with phenobarbital until he reached 20 years of age. An MRI scan of his brain highlighted mild enlargement of the ventricles and significant widespread cortical thinning, while his electroencephalogram revealed a generalized epileptic activity pattern[13].

In all the cases mentioned above, we notice the characteristic phenotypic variability of the syndrome and the fact that the therapeutic approach to epileptic manifestations required customization of the treatment plan. Additionally, we observe in the specialized literature that the control of epileptic manifestations is closely correlated with the severity of autistic symptoms, suggesting that effective control of epileptic seizures also leads to an improvement in symptoms of the autism spectrum[1,12].

TREATMENT AND PROGNOSIS

In this specific instance, the patient needed a comprehensive treatment plan involving multiple antiepileptic medication. With the 16p microduplication syndrome, 29% of cases exhibit epilepsy and often demand intricate antiepileptic drug combinations to manage their symptoms. Given the unique aspects of each case, it's crucial for the patient to undergo a holistic, multidisciplinary treatment strategy. We emphasize that early genetic detection and meticulous management of symptoms should be the primary focus for the medical team. This can promote the patient's neuropsychomotor development and potentially prevent the onset of more severe clinical manifestations[12].

CONCLUSION

The 16p11.2-p12.2 microduplication syndrome is a genetic neurodevelopmental disorder with various symptoms that necessitates a comprehensive multidisciplinary approach. If epilepsy is present, the primary focus should be on the specialized neurological management of epileptic symptoms. We advise genetic consultation for both the patient and their family.

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REFERENCES

1. Tabet, AC., Pilorge, M., Delorme, R. et al. Autism multiplex family with 16p11.2p12.2 microduplication syndrome in monozygotic twins and distal 16p11.2 deletion in their brother. Eur J Hum Genet 20, 540–546 (2012).
2. Barber JC, Hall V, Maloney VK, Huang S, Roberts AM, Brady AF, Foulds N, Bewes B, Volleth M, Liehr T, Mehnert K, Bateman M, White H. 16p11.2-p12.2 duplication syndrome; a genomic condition differentiated from euchromatic variation of 16p11.2. Eur J Hum Genet. 2013 Feb;21(2):182-9. doi: 10.1038/ejhg.2012.144. Epub 2012 Jul 25. PMID: 22828807; PMCID: PMC3548261.
3. Dell'Edera D, Dilucca C, Allegretti A, Simone F, Lupo MG, Liccese C, Davanzo R. 16p11.2 microdeletion syndrome: a case report. J Med Case Rep. 2018 Apr 3;12(1):90. doi: 10.1186/s13256-018-1587-1. PMID: 29609622; PMCID: PMC5881179.
4. Ravinesh A. Kumar, Samer KaraMohamed, Jyotsna Sudi, Donald F. Conrad, Camille Brune, Judith A. Badner, T. Conrad Gilliam, Norma J. Nowak, Edwin H. Cook, William B. Dobyns, Susan L. Christian, Recurrent 16p11.2 microdeletions in autism, Human Molecular Genetics, Volume 17, Issue 4, 14 February 2008, Pages 628–638,
5. Weiss LA, Shen Y, Korn JM, Arking DE, Miller DT, Fossdal R, Saemundsen E, Stefansson H, Ferreira MA, Green T, Platt OS. Association between microdeletion and microduplication at 16p11. 2 and autism. New England Journal of Medicine. 2008 Feb 14;358(7):667–75.
6. Shinawi M, Liu P, Kang SH, Shen J, Belmont JW, Scott DA, Probst FJ, Craigen WJ, Graham BH, Pursley A, Clark G. Recurrent reciprocal 16p11. 2 rearrangements associated with global developmental delay, behavioural problems, dysmorphism, epilepsy, and abnormal head size. Journal of medical genetics. 2010 May 1;47(5):332-41.
7. Bijlsma EK, Gijsbers AC, Schuurs-Hoeijmakers JH, Van Haeringen A, van de Putte DF, Anderlid BM, Lundin J, Lapunzina P, Jurado LP, Delle Chiaie BA, Loeys B. Extending the phenotype of recurrent rearrangements of 16p11. 2: deletions in mentally retarded patients without autism and in normal individuals. European journal of medical genetics. 2009 Mar 1;52(2-3):77–87.
8. Fernandez BA, Roberts W, Chung B, Weksberg R, Meyn S, Szatmari P, Joseph-George AM, MacKay S, Whitten K, Noble B, Vardy C. Phenotypic spectrum associated with de novo and inherited deletions and duplications at 16p11. 2 in individuals ascertained for diagnosis of autism spectrum disorder. Journal of medical genetics. 2010 Mar 1;47(3):195–203.
9. McCarthy SE, Makarov V, Kirov G, Addington AM, McClellan J, Yoon S, Perkins DO, Dickel DE, Kusenda M, Krastoshevsky O, Krause V. Microduplications of 16p11. 2 are associated with schizophrenia. Nature genetics. 2009 Nov;41(11):1223–7.
10. Walters RG, Jacquemont S, Valsesia A, de Smith AJ, Martinet D, Andersson J, Falchi M, Chen F, Andrieux J, Lobbens S, Delobel B. A new highly penetrant form of obesity due to deletions on chromosome 16p11. 2. Nature. 2010 Feb 4;463(7281):671–5.
11. Jacquemont S, Reymond A, Zufferey F, Harewood L, Walters RG, Kutalik Z, Martinet D, Shen Y, Valsesia A, Beckmann ND, Thorleifsson G. Mirror extreme BMI phenotypes associated with gene dosage at the chromosome 16p11. 2 locus. Nature. 2011 Oct 6;478(7367):97–102.
12. Lengyel A, Pinti É, Pikó H, Jávorszky E, David D, Tihanyi M, Gönczi É, Kiss E, Tóth Z, Tory K, Fekete G, Haltrich I. Clinical and genetic findings in Hungarian pediatric patients carrying chromosome 16p copy number variants and a review of the literature. Eur J Med Genet. 2020 Oct;63(10):104027. doi: 10.1016/j.ejmg.2020.104027. Epub 2020 Aug 3. PMID: 32758661.
13. Finelli P, Natacci F, Bonati MT, *et al.,* FISH characterisation of an identical (16)(p11.2p12.2) tandem duplication in two unrelated patients with autistic behaviour, Journal of Medical Genetics 2004;41:e90.