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CASE REPORT Open Access

Is it worth a CGH array? MBD5 haploinsufficiency and clinical variability in MBD5-associated neurodevelopmental disorder: a case report

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Abstract

Background MBD5 (methyl-CpG-binding domain protein 5) haploinsufficiency is a rare genetic disorder primarily characterized by intellectual disability, speech delay, and various physical and behavioral anomalies. This case is noteworthy due to the presentation of previously unreported symptoms, which contributes to the expanding clinical spectrum of the disorder.

Case presentation We present a 16-year-old girl with a mild phenotype of MBD5 haploinsufficiency, including a clinical history of epileptic seizures responsive to treatment, generalized anxiety, selective mutism, obsessive traits, and aggressive behavior. In addition, she exhibited subclinical hypothyroidism, hyperprolactinemia, and six hypochromic skin spots, which have not been documented in prior literature. She underwent an inconclusive target next-generation sequencing (NGS) of 43 known epilepsy-associated genes. Further investigation using array-CGH revealed a mosaic 407 kb deletion at 2q23.1 encompassing the *MBD5* (methyl-CpG-binding domain protein 5) gene.

Conclusions This case emphasizes the role of array-CGH in the diagnosis of cryptogenic cases and the importance of reporting rare Copy Number Variants (CNVs) to refine the phenotypic descriptions of microdeletion/microduplication syndromes.

Keywords MBD5 haploinsufficiency, MAND, Neuropsychiatric disorder, Array-CGH

Background

MBD5 haploinsufficiency is a rare genetic disorder with approximately 50 cases described in the literature to date; the prevalence is unknown and may be higher than observed due to undiagnosed cases. [1, 2]. It has been identified in approximately 1% of individuals with autism spectrum disorder, based on analysis of 4808 cases across three cohorts [1]. *MBD5* (methyl-CpG-binding domain protein 5) is a gene on chromosome 2q23.1 encoding a protein of the methyl-CpG-binding domain family involved in epigenetic regulation [1, 2].

Large and intragenic deletions (including those encompassing noncoding exons) or duplications, coding sequence variants and more rarely apparently balanced complex rearrangements affecting this gene are

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highly penetrant and cause a broad phenotypic spectrum defined as "MBD5-associated neurodevelopmental disorder" (MAND) which is characterized by impaired neurodevelopment, cognition and behavior [1].

Here we discuss a patient showing mild phenotype and additional symptoms not previously associated with MAND.

Case presentation

The patient is a 16-year-old girl born from non-consanguineous parents; the family included two other healthy sisters. Within her family history there are some neurological and psychiatric events. One of her sisters experienced mild speech delay in her early years, no longer present. Her maternal grandparents suffer from major depressive disorder currently treated with antidepressant drugs; the grandfather attempted suicide twice during his life. A grandfather's brother died by suicide. One of the grandmother's sisters suffers from schizophrenia.

Our patient was born at full term from a regular pregnancy by cesarean delivery due to extraction difficulties. Her weight and height growth were regular, as well as the acquisition of motor developmental stages. During the first year of life, she exhibited poor babbling; she spoke her first words at 18 months and formed her first sentences when she was three. At that time two tests to assess her speech skills (MacArthur test and first language test, Axia 1995) showed lower than normal abilities both in language comprehension and language production, several pronunciation difficulties and limited vocabulary, well managed with speech therapy.

At 2 years, she presented the first non-febrile focal epileptic seizures with secondary generalization. Since then, she encountered monthly epileptic seizures carbamazepine-resistant in the following 6 months. Carbamazepine was later replaced by valproate with seizure freedom; therapy was gradually discontinued at 13 years.

At 8 years, a diagnosis of selective mutism comorbid with generalized anxiety disorder, also reflected in the results of the Child Behavior Checklist (CBCL) score, was established according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) criteria; furthermore, the presence and progressive worsening of obsessive traits and aggressive and self-injurious behavior, required treatment with aripiprazole at 14 years.

At the age of 12 due to poor nighttime sleep quality, clobazam was introduced with good response. Her physical examination revealed no dysmorphic features or other abnormalities; six hypochromic skin spots and speckled lentiginous nevus under the right scapula were noted.

The first strong clinical hypothesis was tuberous sclerosis, requiring periodical medical check-ups that yielded normal results.

Multiple Electroencephalograms (EEGs) revealed generalized epileptiform abnormalities, while all Brain Magnetic Resonance Imaging (MRI) came back negative. At blood tests subclinical hypothyroidism and hyperprolactinemia were diagnosed.

Cognitive ability assessments was done at 2, 7 and 10 years, including the Stanford–Binet test, Leiter-R scale and the WISC-IV (Wechsler Intelligence Scale for Children, fourth edition), fell within the normal range. However, the WISC-IV scale administered at the age of 12 indicated the presence of mild intellectual disability, with a global IQ (Intelligence Quotient) of 50.

A panel of 43 epilepsy-associated genes, including *TSC1* and *TSC2*, responsible for tuberous sclerosis, was analyzed through Next Generation Sequencing (NGS) at the age of eight without significant results.

At the age of 11, a ISCA 8×60 K, array-CGH assay (Agilent Technologies) identified a 407 kb mosaic deletion of the 2q23.1 region (arr[GRCh37] 2q23.1(148743880_149151023)×1–2), partially involving the *MBD5* (non-coding exons 1–5) and ORC4 genes and affecting approximately 44% of the patient's blood cells.

This genetic finding led to the diagnosis of MBD5 haploinsufficiency.

Conclusions

MBD5 haploinsufficiency is a rare genetic disorder whose clinical features are summarized in Table 1(1A). The main feature of this syndrome is intellectual disability with a pronounced speech delay; additional features are a coarse face, short stature, microcephaly, epileptic seizures, broad-based gait, disturbed sleep patterns and behavioral abnormalities [3, 4].

The clinical phenotype of our patient, consistent with the diagnosis of MBD5 haploinsufficiency, is summarized in Table 1(1B) and compared to the common features of the syndrome in Table 1(1A). Worth mentioning is the presence of subclinical hypothyroidism, hyperprolactinemia and six hypochromic skin spots, which have not been previously reported in the literature; however, due to the lack of functional studies, we are unable to determine their pathogenic in MBD5-related disorders.

Regarding instrumental findings described in the literature, most EEG patterns are nonspecific, and focal spikes and spike-wave complexes occur in some individuals [1, 2, 4, 5]; many different findings have been described for brain MRIs. Our patient confirms the absence of specific EEG patterns and brain MRI features.

While the literature described a severe-to-moderate cognitive impairment from the beginning, our patient

Table 1 Clinical and instrumental findings: (1A) literature findings; (1B) observed in our patient

1A [1, 2–5, 8–10]	1B
Intellectual disability (severe or moderate)	Mild intellectual disability
Lack of speech or severe speech impairment (of both receptive and expressive skills)	Speech delay with limited vocabulary and mild impairment on both receptive and expressive language
Short stature, microcephaly	Absent in our patient
Cardiovascular abnormalities (atrial septal defect, ventricular septal defect and pulmonary stenosis)	Absent in our patient
Urogenital abnormalities	Absent in our patient
Gross or fine motility delay, broad-based ataxic gait, poor coordination	Absent in our patient
Infantile hypotonia, infantile difficulties in feeding	Absent in our patient
Epileptic seizures, often severe and drug resistant (complex partial seizures, atonic seizures, absence seizures, febrile seizures, generalized tonic–clonic seizures, generalized tonic seizures, partial seizures, secondary generalized seizures)	Afebrile focal epileptic seizures with secondary generalization, more often during sleep, responsive to valproic acid treatment
Dysmorphic features (broad forehead, structural nasal abnormalities, outer ear abnormalities, thick or arched eyebrows, downturned mouth corners, everted lower lip and thin upper lip)	Absent in our patient
Skeletal abnormalities (small hands and feet, fifth finger clinodactyly and brachydactyly, hip dysplasia, joint laxity, scoliosis)	Absent in our patient
Behavioral issues (autistic features such as ripetitive, stereotypic behavior; distractability/short attention span; aggressive and self-injurious behaviors, self-mutilation, hyperphagia)	Generalized anxiety, selective mutism, short attention span, obsessive traits and aggressive and self-injurious behaviors
Sleep disturbances (waking 6–8 times per night, apparent night terrors in the early part of the sleep, waking in the early hours of the morning)	Difficulty in falling asleep and multiple nocturnal awakenings (limited response to melatonin and clobazam)
As patterns (nonspecific EEG patterns, focal spikes and spike-wave complexes)	Diffuse bilateral epileptic anomalies
MRI findings both positive (myelination delay, brain atrophy ventricular asymmetry, focal cortical abnormalities, small cerebellar vermis, white matter abnormalities, thinning of posterior corpus callosum and frontal region hypoplasia) and negative	Normal MRIs
Not described in the literature	Hyperprolactinemia
Not described in the literature	Subclinical hypothyroidism
Not described in the literature	Hypochromic skin spots (6)

presented with normal IQ at first evaluation, and obtained a lower result (IQ 50) during the last administration of WISC-IV. In our opinion, this result is attributable to her neurobehavioral decline, given WISC-IV susceptibility to response latency. It is worth observing that emotional factors (e.g., sleep disturbances and anxiety) have likely contributed to worsen her cognitive performance.

Several *MBD5* deletions involving exclusively the non-coding exons are reported in clinical databases (ClinGen, ClinVar, DECIPHER, and GeneReviews) and literature [2, 7, 9]). When tested, *MBD5* transcript levels turned out to be reduced in patients with deletions of non-coding exons 1 and 2, confirming haploinsufficiency. Since no genotype–phenotype correlations have been reported [1] the milder phenotype observed in our patient, with the manifestation of only some symptoms commonly associated with the MBD5 haploinsufficiency, could be at least partly explained by the mosaicism for the *MBD5* deletion, affecting about 44% of blood cells. Mosaic deletions are reported in several families with no clinical anomalies, mild–moderate intellectual disability, or neuropsychiatric problems in transmitting parents and seizure and moderate–severe cognitive involvement in affected children [6, 7].These reports suggest that mosaic alterations could be less penetrant than constitutional MBD5 haploinsufficiency and multiple and yet unidentified factors, including the percentage of affected cells in not accessible target tissues, could influence the resulting phenotype.

We aim to share information about a newly diagnosed patient with MBD5 haploinsufficiency. We recognize the importance of describing cases with rare Copy Number Variants (CNVs) to help define the phenotypic spectrum and understand the role of genes involved in recently discovered genetic syndromes.

With the increasing attention given to MAND, we provide the clinical and instrumental data of our patient, highlighting aspects that differ from the clinical features described in the literature.

This case confirms the important role of array-CGH in the diagnostic flow chart of cryptogenic patients with epilepsy and neuropsychiatric disorders.

The present findings have some limitations, including the absence of functional studies, necessary for precise genotype–phenotype correlation, and the lack of additional affected family members to corroborate our statements.

Abbreviations

CBCL	Child Behavior Checklist
CNVs	Copy Number Variants
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
EEG	Electroencephalograms
IQ	Intelligence Quotient
MAND	MBD5-associated neurodevelopmental disorder
MBD5	Methyl-CpG-binding domain protein 5
MRI	Magnetic Resonance Imaging
NGS	Next Generation Sequencing
WISC-IV	Wechsler Intelligence Scale for Children—Fourth Edition

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Author contributions
Dr. T.F. was responsible for the design, literature search, clinical studies, data acquisition, manuscript preparation, manuscript editing, and manuscript review. Dr. M.T. was responsible for concepts, design, definition of intellectual content, literature search, clinical studies, data acquisition, manuscript editing, and manuscript review. Dr. L.G.J. was responsible for literature search, data acquisition, and manuscript preparation. Dr. M.P. was responsible for literature search, data analysis, manuscript editing, and manuscript review. Prof. S.M. was responsible for data acquisition, data analysis, manuscript editing, and served as a guarantor. Prof. C.D.M. was responsible for manuscript editing, manuscript review, and served as a guarantor.

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Availability of data and materials
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Declarations

Ethics approval and consent to participate
This study involves human participants but an Ethics Committee exempted this study. The Ethics Committee has exempted this study as it is a descriptive clinical case and no experimentation has been planned.

Consent for publication
The patient has provided written consent for the publication of this article.

Competing interests
The authors declare that they have no competing interests.

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