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Case Report

"Neurodevelopmental Disorder with Microcephaly, Epilepsy, and Brain Atrophy" with a Novel Mutation

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Abstract

"Neurodevelopmental disorder with microcephaly, epilepsy, and brain atrophy" is a newly described disorder related to homozygous mutations in TRAPPC6B gene. Although nonspecific, the features of this disorder appear to have a characteristic course of postnatal progressive microcephaly that should raise the suspicion of this disorder. To the best of our knowledge, only eight cases were published in the literature. Here, we report a new case with a novel mutation and compare the clinical findings to the published cases. This case was not picked up by whole-exome sequencing but rather by whole-genome sequencing, emphasizing the importance of pursuing an etiological diagnosis in patients with otherwise unexplained progressive neurological disorders.

Keywords: Brain atrophy, epilepsy, neurodevelopmental disorder with microcephaly

Introduction

Neurodevelopmental disorder with microcephaly, epilepsy, and brain atrophy (NEDMEBA) OMIM# 617862 is a recently described disorder associated with autosomal-recessive intellectual disability.[1,2] Global developmental delay is a common disorder, affecting about 1%–3% of children.[3] Routine cytogenetic testing has been recommended even in the absence of dysmorphic features since the diagnostic yield is as high as 3.5%–10%.[3] However, the development of clinical whole-exome and whole-genome sequencing (WGS) has further increased the diagnostic yield of genetic studies[4,5] in addition to enabling the identification of new genetic mutations not previously linked to clinical disorders.[5,6] Recently, Marin-Valencia *et al*. first described a new disorder of "autosomal-recessive NEDMEBA associated with homozygous mutations in TRAPPC6B gene in six children from three unrelated consanguineous families from different parts of Egypt and performed functional studies on the mutations providing evidence of the role of TRAPPC6B gene dysfunction to the phenotype.[1] We report a new case of this rare genetic cause of developmental delay with microcephaly, epilepsy, and brain atrophy related to a novel intronic homozygous mutation in TRAPPC6B gene. We aim to reaffirm the phenotypic spectrum of this disorder, as well as raise awareness about this condition in children with otherwise unexplained neurodevelopmental disorder with comorbidities.

Case Report

A 5-year-old Pakistani male with neurodevelopmental delay and severe intellectual disability was referred to our clinic for the evaluation due to reported neonatal seizures and "perinatal complications." The patient was the product of full-term gestation through normal vaginal delivery with a birth weight of 3.5 kg (50 percentile), length of 51 cm (69 percentile), and head circumference of 33 cm (6.5 percentile). Parents are consanguineous. At 5 years of age, he has no language development except for monosyllabic sounds (Ma, Da), he does not understand simple commands, he recognizes his parents but has poor social interaction, and is hyperactive while awake with nonpurposeful nonstereotypic head, hand, and leg movements. He can sit from the supine position but cannot stand or walk.

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Physical examination revealed an alert child who is not oriented, has dysmorphic facial features, including progressive microcephaly, almond-shaped eyes, in addition to inverted wide-spaced nipples [Figure 1], lower abdomen wall fat pads, and long thumbs. The heart, lungs, abdomen, and genitourinary examination are unremarkable. His neurological examination is remarkable for axial and limb hypotonia, markedly diminished deep-tendon reflexes, and inability to stand or take steps.

Magnetic resonance imaging (MRI) of the brain [Figure 2] revealed a thin corpus callosum with periventricular and deep white matter signal hyperintensity reported to be "suggestive of perinatal hypoxic-ischemic changes;" however, there was no substantiated evidence of hypoxia/ischemia at birth. Nerve conduction study was normal for age; however, his EMG revealed nonspecific chronic neurogenic features. A metabolic screen, including plasma amino acids, urine organic acids, plasma acylcarnitine, leukocyte lysosomal enzymes as well as mucopolysacchride screen was within normal for age. Prader-Willi fluorescence *in situ* hybridization probe was negative. Based on the negative initial investigations, whole-exome sequencing (WES) was performed and was reported as negative. However, WGS identified a homozygous likely pathogenic variant c. 149 + 2T >A in Intron 2 in the TRAPPC6B gene, which is consistent with the genetic diagnosis of "autosomal recessive NEDMEBA." This variant was found on the WES but not reported at the time due to lack of clinical reports of its pathogenic significance. The revaluation of parents previous WES has confirmed their carrier status.

Discussion

Pathology and genetics

TRAPPC6B gene codes the β subunit of transport protein particle (TRAPP) protein C6, which is part of the TRAPP complex involved in tethering mechanism involved in vesicle transport.[7] Kümmel *et al*. speculate that the TPC6 and BET3 (another TRAPP subunit) interact to form an *in vivo* subcomplex that could represent the starting point for complex assembly at the Golgi membrane.[7] Harripaul *et al*. reported loss-of-function mutations in TRAPPC6B among nine new autosomal recessive intellectual disability genes[2] and have noted that these genes are highly expressed in the prenatal brain. It is logical to speculate that the function of TRAPPC6B as part of TRAPP complex and its role in vesicle transport are critical to cell trafficking during the critical period of brain development. However, Marin-Valencia *et al*. reported that fibroblasts from affected patients did not show any obvious abnormalities in the Golgi apparatus, but the expression studies in knock out zebrafish model showed decreased cell survival and increased number of apoptotic cells.[1] This may well correlate with some of the clinical features of the microcephaly and thin corpus callosum.

Clinical features

NEDMEBA is a neurodevelopmental disorder associated with microcephaly, epilepsy, and brain atrophy. The main clinical features involve the central nervous system, psychomotor development, and growth.

Dysmorphology and extra-neurological involvement

No frank dysmorphic features are reported with this condition. However, we observed that the patient described here does have prominent ears, almond-shaped eyes, inverted wide-spaced nipples, and relatively long thumbs. Marin-Valencia *et al*. reported prominent ears in their cohort but attributed that to the microcephaly. The main extra-neurological manifestation is strabismus.

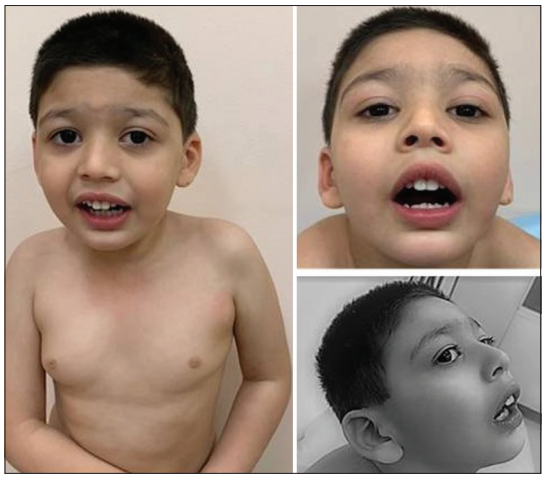

Figure 1: Microcephaly with mild retrognathia, prominent ears, almond-shaped eyes, wide-spaced nipples, and fat pads

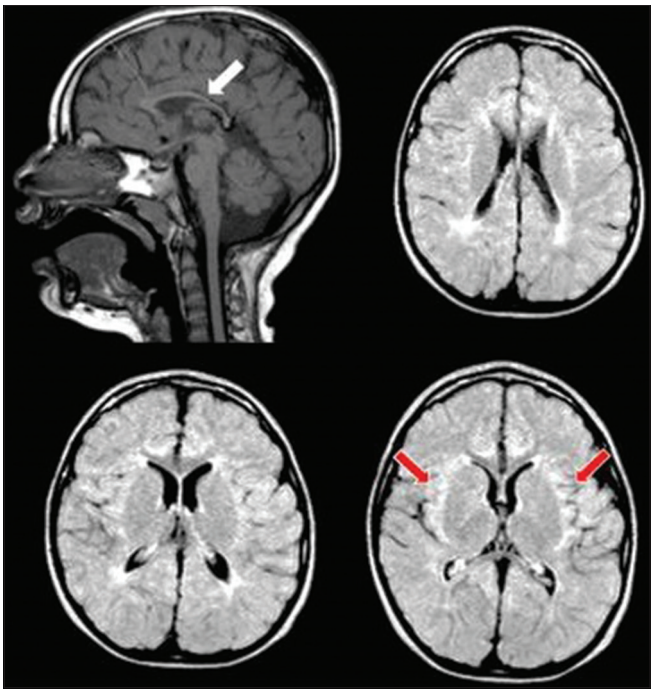

Figure 2: Brain magnetic resonance imaging showing thin corpus callosum (white arrow sagittal view), and periventricular hyperintense T2 signal on axial FLAIR, as well as an external capsule (red arrows) hyperintense T2 signals

Table 1: Comparison of clinical and diagnostic features of the present case and previous published case series

	Marin-Valencia *et al*. Study	The present case
Demographics	Family 1: Male 8yrs, Female 3 yrs	Male 5 yrs
	Family 2: Male 10 yr, Female 12 yrs	
	Family 3: Male 10yrs, Male 2 yrs	
Consanguinity	Yes	Yes
Clinical features	Microcephaly	Microcephaly
	Global developmental delay	Global developmental delay
	Intellectual disability	Intellectual disability
	Autistic features	Autistic features
	Generalized tonic clonic seizures	NO SEIZURES
	No obvious facial dysmorphism besides prominent ears due to microcephaly	Dysmorphism: almond shaped eyes, inverted wide spaced nipples, lower abdomen wall fat pads , long thumbs
Growth parameters	Small head circumference (> 3SD)	Small head circumference (> 3SD)
	Short stature (-2 to -3 SD)	Short stature (-1 to -2 SD)
	Weight average for age and gender	Underweight (-2 to -3 SD)
Neurological exam	Generalized hypotonia	Generalized hypotonia
	Generalized weakness (normal muscle bulk)	Normal muscle bulk
	Brisk deep tendon reflexes in all limbs	Deep tendon reflexes diminished in all limbs
	Ataxic gait	Non- ambulatory
	Mild horizontal nystagmus (3 pts)	Normal ophthalmological exam
	Extrapyramidal signs:	Extrapyramidal signs:
	Resting and postural hand tremors (4 pts)	Head nodding
	Jaw and perioral dystonia (1 pt)	
Brain MRI	Cortical atrophy	Thin corpus callosum
	Thin corpus callosum	Abnormal white matter signal changes
	Cerebellar and brainstem atrophy	
Neurophysiology	EEG (4 pts): Intermittent multifocal epileptiform discharges	NCS: normal, EMG: features of chronic denervation
Clinical course	Worsening of ataxic gait, loss of psychomotor skills, become overall more dependent (2pts in early 20s)	Stable clinical course, no regression
	Worsening MRI structural findings over time	MRI brain not repeated

Features in bold are distinctive in the present patient

Neurological manifestations

Progressive microcephaly is an important clinical feature reported in all cases. These children also manifest severe intellectual disability, lack of speech development, epilepsy, autistic features, hypotonia, and ataxia. Our patient did not manifest any seizures yet, although he had undocumented report of "neonatal convulsions." His most prominent neurological manifestations are the lack of speech and significant hypotonia/ataxia.

Brain imaging

Brain MRI revealed a thin corpus callosum, cortical atrophy, brainstem, and cerebellar atrophy. These findings worsened overtime on repeated brain imaging in some of the patients.[1] The patient, in this case, did not undergo repeat imaging due to no clinical indication. In this case, however, abnormal T2 hyperintensities in the deep white matter were also present, suggesting the MRI abnormalities in patients with TRAPPC6B mutations may have a wider spectrum of neuroradiological abnormalities than earlier reported.

Diagnosis

To date, all eight published cases, six by Marin-Valencia *et al*. and two by Harripaul *et al*., were diagnosed by WES,[1,2] suggesting that the clinical features are relatively nonspecific. Another recently published case by Nair *et al*.[8] was also diagnosed by WES showing a homozygous likely pathogenic c. 23T >A variant in exon 1. The case reported here shows a phenotypic expression and clinical course very consistent with the published cases, specifically the postnatal progressive microcephaly and thin corpus callosum and brain atrophy [Table 1]. It is probably too early in the course of discovery of this disorder to recommend single gene testing as the clinical phenotype may later prove to be genetically heterogeneous. Moreover, this patient showed an intronic mutation that could be missed on WES. Hence, we suggest that WGS may be the most appropriate diagnostic tool in children with a compatible clinical picture who otherwise do not have an etiological diagnosis for their progressive postnatal microcephaly, intellectual disability, and lack of speech development.

Management

There is no known specific treatment at this stage. The management is symptomatic and supportive with focus on early intervention.

Follow-up

Patients should be followed up for growth failure, progressive motor difficulties, strabismus, as well as autistic spectrum

disorder. Parents should be offered testing for heterozygous status to inform the risk of recurrence in future pregnancies.

Prognosis

As a relatively new neurodegenerative disorder, it remains unclear what the long-term outcome of these children is likely to be, although the early manifestation of severe progressive microcephaly and intellectual disability indicate a high risk for continued regression and long-term disability.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's guardian has given his consent for patient's images and other clinical information to be reported in the journal. He understands that name and initial will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Authors' contributions

Both authors contributed to the preparation, revision, and approval of the final version.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

A written consent was obtained from the father for photographs and reporting the case.

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