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Short communication

MEF2C-related epilepsy: Delineating the phenotypic spectrum from a novel mutation and literature review

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ABSTRACT

Purpose: MEF2C-related epilepsy has been poorly described in the literature, despite a consistent *MEF2C* haploinsufficiency phenotype characterized by severe language impairment and motor delay (MIM# 613443). We aimed to delineate the spectrum of electroclinical manifestations of MEF2C-related epilepsy from an illustrative case and literature review.

Methods: A retrospective chart review of our case was performed followed by a literature review on PubMed and OMIM. Publications including patients with *MEF2C* pathogenic, likely pathogenic variants, or microdeletions without involvement of other genes were selected.

Results: The index case is a 2-year-old male with global developmental delay who presented at 7 months with atypical febrile seizures, generalized myoclonias, and focal impaired awareness seizures. Neuroimaging studies were unremarkable and electroencephalograms showed high voltage 200-400uV, 2–2.5 Hz generalized spike-and-waves and polyspikes with alternating frontal predominance, and multifocal spike-and-slow waves. Whole exome sequencing showed an unreported *de novo* likely pathogenic variant in the *MEF2C* gene c.236 G > C (p.Arg79Pro). Data from ten additional publications including 22 patients were gathered. From the 23 patients in total, 19 (82%) had seizures. Febrile seizures were most common, but myoclonic, focal-onset and generalized seizures were also reported. Electroencephalogram findings were described in eleven, and nine (82%) showed epileptiform abnormalities.

Conclusion: MEF2C-related epilepsy may be described as a spectrum of manifestations including febrile seizures, myoclonia, and focal-onset or generalized seizures. Electroencephalogram is consistently abnormal, showing findings such as background slowing, multifocal and generalized epileptiform discharges and polyspikes. It remains unclear whether most patients are responsive or refractory to treatment with anti-epileptic medications.

1. Introduction

MEF2C haploinsufficiency has been described in the literature over the past decade, with the majority of patients harbouring 5q14.3 microdeletions (MIM# 613443, mental retardation, stereotypic movements, epilepsy, and/or cerebral malformations) [1]. These patients typically present with severely impaired expressive language, gross motor delay and epilepsy.[2] The phenotype may resemble Rett's syndrome in some cases, with stereotypic behaviour, particularly hand flapping, but no microcephaly or neuroregression [3]. To the best of our knowledge, only 22 cases of *MEF2C* pathogenic and likely pathogenic variants or microdeletions without involvement of other contiguous or distant genes have been reported [1–10]. So far, the electroclinical patterns in *MEF2C* haploinsufficiency have been infrequently and inconsistently described. Thus, given the paucity of data related to seizure phenotype and electrographic features in this rare condition, we aim to review the previously reported cases and describe in details the seizure history and electroencephalogram (EEG) abnormalities of a patient who was found to have a *de novo* previously unreported likely pathogenic variant in the *MEF2C* gene. This may allow us to further delineate our knowledge of the electroclinical spectrum of manifestations related to *MEF2C* mutations.

2. Methods

A retrospective chart review was completed and details were

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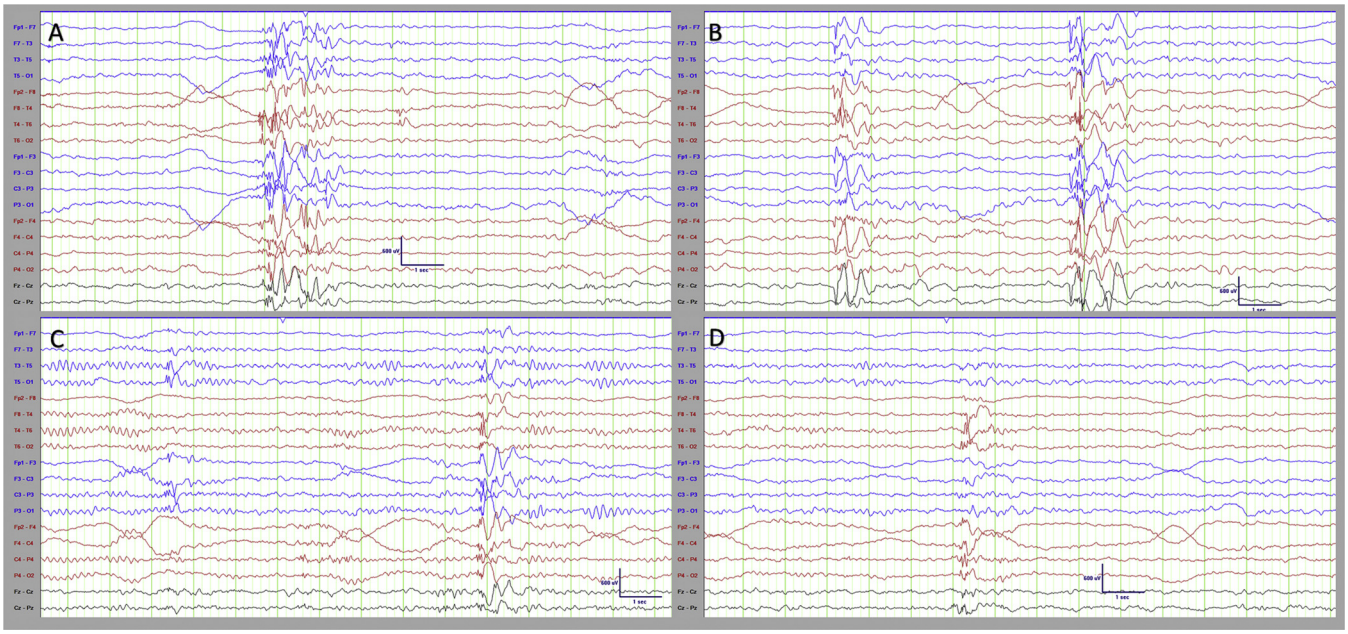

Fig. 1. Generalized high amplitude (200–500 uV) irregular 2–2.5 Hz polyspike-and-slow wave discharges (A, B and C). Independent right temporal spike-and-slow wave discharge located at T4 (A). Polyspikes and spike-and-wave discharges with left hemispheric distribution (C). Independent polyspikes and-wave discharges noted with right hemispheric distribution (D). Filters: LFF 1 Hz, HFF 70 Hz, notch 60 Hz, sensitivity 30 u V/mm, timebase 30 mm/sec.

collected with regard to the epilepsy history, developmental and past medical history, family history, physical examination, treatments and results from investigations. Consent was obtained from the patient's caregivers in accordance with our Research Ethics Board at The Hospital for Sick Children, Toronto, Ontario, Canada. The literature review was performed on PubMed and OMIM using the terms "MEF2C gene" and "epilepsy". Publications in English, including patients with *MEF2C* pathogenic, likely pathogenic variants, or microdeletions without involvement of other contiguous or distant genes were included. Demographic and genetic data, seizure history, EEG and neuroimaging reports were extracted from all previously reported patients.

3. Results

3.1. Case description

The index case, a male currently 2 years old, was born at 38 weeks to unrelated parents of Italian ancestry. Pregnancy was unremarkable and was followed by an uneventful spontaneous vaginal delivery. He presented at 7 months of age with a cluster of atypical febrile seizures in the context of a respiratory tract infection. These atypical febrile seizures consisted of focal motor seizures with unilateral but alternating left- and right-sided clonic activity, generalized myoclonias, and impaired awareness lasting two minutes each. At that time, he also had global developmental delay. He was not able to sit or roll over, had no non-verbal communication skills and was not able to imitate or babble. At the age of 7 months, his neurological examination revealed the following: head circumference was 44 cm (10^{th} percentile) and axial hypotonia but no other abnormalities; no dysmorphic features. Investigations included: Neuroimaging - brain MRI with age-appropriate myelination and small areas of non-specific T2 white matter hyperintensity in the parietal lobes; MR spectroscopy was unremarkable. Genetic investigation included 46 XY karyotype and normal results in methylation testing for the *SNRPN* gene, *FMR1* repeats, and microarray.

At 7 months of age, the child was started on Levetiracetam 30 mg/kg/day, and required increasing doses up to 60 mg/kg/day due to breakthrough atypical febrile and afebrile seizures, characterized by impaired awareness, autonomic features (pallor, hypopnea and cyanosis), and mild motor manifestations with brief alternating unilateral clonic movements and generalized myoclonias. Since 7 months, parents have also observed an exaggerated startle reaction to loud noises or sudden sensory stimulation.

The first EEG at the age of 7 months revealed high voltage 200–400uV, 2–2.5 Hz generalized spike-and-waves and polyspikes with alternating right and left frontal predominance. The background activity was 5 Hz theta and reactive to eye closure. Follow up EEGs at the ages of 12 and 15 months have shown independent bilateral multifocal spike-and-slow wave discharges, and high voltage, 200–500uV, generalized 2–2.5 Hz polyspikes/spike-and-slow waves (Fig. 1). The background rhythm is still appropriate for the patient's age, 6–7 Hz, reactive to eye closure. Stage N1 and N2 sleep have been well characterized with no abnormalities.

The child is currently 2 years old and continues to exhibit global developmental delay with low axial tone. He is able sit and stand up independently, but cannot walk. He does not show a hand preference or have a pincer grasp. He is able to vocalize, but has no intelligible words and is unable to follow one-step commands. Cognitively, his functions at the level of a 9-month old.

Following the negative initial genetic work-up, the child underwent whole exome sequencing, which revealed a *de novo* heterozygous likely pathogenic variant c.236 G > C (p.Arg79Pro) in the *MEF2C* gene. This variant is not present in large population cohorts, and is a non-conservative amino acid substitution, which is likely to impact secondary protein structure. In silico analysis supported a deleterious effect.

3.2. Literature review

Ten publications including 22 patients were selected (Table 1). [1–10] Out of these 23 patients (including the child in this report) harbouring *MEF2C* pathogenic, likely pathogenic variants, or microdeletions encompassing exclusively the *MEF2C* gene, 19 have had seizures (82%). Seizures were reported in the first 12 months of life in 12 of the 19 patients (63%). Mean age of seizure onset was 13.5 months (SD ± 8.1, median 12), ranging from 3 to 36 months. Febrile seizures were the most common seizure type, in 43% (10/23) of patients.

Table 1
Patients reported with *MEF2C* pathogenic and likely pathogenic variants, or microdeletions exclusively encompassing the *MEF2C* gene.

Case number	Sex/Age at evaluation	Genetic defect	Epilepsy phenotype	EEG description	Brain MRI	Reference
1	M/ 2y	De novo, likely pathogenic heterozygous variant, *MEF2C*: c.236 G > C (p.Arg79Pro).	Atypical FS starting at 7 months, focal impaired awareness motor seizures with clonic manifestations, autonomic features, and generalized myoclonias. Partial response to LEV.	Background within the normal limits for the patient's age. Normal sleep architecture. Generalized high amplitude (200-500 uV) irregular 2-2.5 Hz polyspike-and-slow wave discharges. Multifocal independent polyspikes/ spike-and-slow waves.	Small areas of non-specific T2 white matter hyperintensity in the parietal lobes.	Current report
2	F/ 5y 9m	De novo, missense variant, MEF2C: c.48C > G (p.Asn16Lys).	Focal seizures starting at 20 months, currently treated with three anti-epileptic medications: VPA, TPM and OXC.	Spike-slow waves at right medial and posterior temporal, with generalization.	Enlargement of frontal subarachnoid space.	Wang et al. [10]
3	F/ 2y 6m	Pathogenic heterozygous variant, MEF2C: c.565C > T (p.Arg189).	Not reported.	"Epileptiform discharge on EEG", but description was not provided.	High T1 and T2 signal at posterior horn of bilateral ventricle.	Wang et al. [10]
4	F/ 2y 4 m	Heterozygous variant, MEF2C: c.334 G > T (p.Glu112).	FS at 9 months.	Normal	Delayed myelination.	Wang et al. [10]
5	M/ 7y 8m	De novo heterozygous variant, MEF2C: c.403-1 G > T.	FS started at 12 months, followed by afebrile seizures characterized by fever-sensitive focal onset seizures, under control with VPA.	Spike and slow waves at right occipital region, and background slowing.	Normal	Wang et al. [10]
6	M/ 6y 4m	De novo pathogenic heterozygous variant, MEG2C: c.766C > T (p.Arg256).	FS starting at 8 months, currently treated with VPA and LEV.	Normal	High T1 and T2 signal around ventricles and septum pellucidum cyst.	Wang et al. [10]
7	F/ 6y 6m	5q14.3q15 del, GC Chr5: 88 098 253-88 592 348.	FS starting in infancy, GTC treated with VPA.	N/A	Frontal cortical atrophy and moderate ventricles enlargement.	Vrečar et al. [9]
8	F/ 9y	5q14.3q15 del, GC Chr5: 88 034 622-88 164 453.	FS starting under the age of 1y, generalized seizures.	"Dysrhythmic" background with high voltage polyspike wave bursts.	Small CC, possible white matter abnormality in occipital lobes.	Vrečar et al. [9]
9	M/ 2y 6m	5q14.3q15 del, GC Chr5: 88 193 289-88 450 318.	FS starting at 15 months, generalized and absence seizures.	N/A	Small splenium of CC, ventricles enlargement.	Vrečar I et al. [9]
10	F/ 3y 1m	De novo, pathogenic heterozygous variant, *MEF2C*: c.220 G > T (p.Glu74Ter, premature stop codon)	FS and afebrile seizures starting under the age of 1y, treated with VPA and PB.	Bilateral temporal slow waves and bilateral parietal spike waves	Normal	Vrečar et al. [9]
11	F/ 3y	*MEF2C* deletion, exons1–2 (MLPA)	Not reported.	N/A	N/A	Vrečar et al. [9]
12	M/ 10y	De novo, pathogenic missense heterozygous variant, *MEF2C*: c.9A > T (p.R3S)	Atypical absence, atonic, myoclonic starting at 26 m. Refractory seizures, currently treated with LTG and Clobazam.	Abnormal and slow background pattern (theta waves with poor reactivity), focal R frontal hemispheric epileptic discharges with frequent generalization	Slight T2 hyperintensity in the periventricular white and enlarged CSF spaces.	Rocha et al. [8]
13	M/ 14y	5q14.3 del (0.01Mb) GC Chr5: 88 110 707-88 278 367.	Not reported.	N/A	Normal	Tanteles et al. [7]
14	Unknown/ 3y	De novo, missense heterozygous variant, *MEF2C*: c.258 G > A (p.E86E)	Seizures reported, but no characteristics provided.	N/A	Delayed myelination	Srivastava S et al. [6]
15	F/ 22m	Pathogenic frameshift variant, *MEF2C*: c.833delT (p.Leu278Terfs)	Myoclonic and atonic seizures starting at 18 m.	Multifocal epileptiform activity and poorly developed AP gradient	Mild thinning of the cortical white matter on T2.	Paciorkowski et al. [5]
16	M/ 30m	5q14.3 del (0.05 Mb), GC Chr5: 880 519 70-881 045 35.	Not reported.	N/A	N/A	Paciorkowski et al. [5]
17	F/ 8y	Pathogenic frameshift heterozygous variant, *MEF2C* c.457delA (p.Asn153ThrfsX33).	Myoclonic and FS starting at 18 m, well controlled on VPA.	Generalized spike and wave, sometimes massive myoclonia sometimes followed by bifrontal spike and slow waves.	Normal.	Bienvenu et al. [4]
18	F/ 3y	De novo, pathogenic missense heterozygous variant, *MEF2C*: c.113 T > A (p.Leu38Gln).	Fist seizure at 10 m, but no further characteristics provided.	N/A	Delayed myelination and generalized lack of white matter bulk.	Zweier M et al. [3]
19	M/ 14y	De novo heterozygous 1-bp duplication of the *MEF2C* gene: 99dupT (p.E34X).	First seizure at 10 m of age, described as complex partial.	N/A	Mildly enlarged ventricles.	Zweier M et al. [3]

(*continued on next page*)

Table 1 (*continued*)

Case number	Sex/Age at evaluation	Genetic defect	Epilepsy phenotype	EEG description	Brain MRI	Reference
20	F/ 7	Pathogenic variant, *MEF2C*: c.226_236del11 (p.H76fsX15).	First seizures described between 3 and 6 m, but no further characteristics provided.	N/A	Normal	Zweier M et al. [3]
21	F/ 10y 5m	De novo, heterozygous missense variant, *MEF2C*:c.80 G > C (p.Gly27Ala).	First seizure at 6 m, but no further characteristics provided.	N/A	Delayed myelination of insular cortices bilaterally	Zweier M et al. [3]
22	F/ 7y	De novo, heterozygous nonsense variant, 683C-G transversion in exon 7 of the *MEF2C* gene, resulting in a ser228-to-ter (S228X) substitution	Well-controlled GTC starting at 9 m, but no further characteristics provided.	N/A	Enlarged ventricles, periventricular T2 hyperintense white matter.	Le Meur N et al. [1]
23	F/ 8y	5q14 del (0.02 Mb), GC: 87 770 283 - 88 051 970.	FS, well-controlled seizures with VPA at the age of 3.	N/A	Abnormal CC	Le Meur N et al. [1]

Abbreviations: CC: corpus callosum; F: female; FS: febrile seizures; GC: genomic coordinates; GTC: generalized tonic-clonic; LEV: levetiracetam; LTG: lamotrigine; M: male; m: month(s); Mb: megabase; OXC: oxcarbazepine; TPM: topiramate; VPA: valproate; y: year(s).

Myoclonic, focal-onset seizures, and generalized seizures have each been observed, in 17% (4/23). Less commonly, atonic seizures have been reported in only 8% (2/23) of patients. Unfortunately, it was not possible to classify the seizures in 17% (4/23) of previously reported patients.

When examining the EEG findings of MEF2C halpoinsufficiency, only 11 of the 23 patients (48%) had reports available (Table 1). The great majority of these patients had an abnormal EEG with epileptiform activity (82%, 9/11). Reported EEG abnormalities include disturbances in background activity, such as background slowing (18%, 2/11) and poor reactivity (9%, 1/11) as well as multifocal and generalized epileptiform discharges.

4. Discussion

MEF2C is a member of the myocyte enhancer factor-2 (MEF2) family of transcription factors, which regulates excitatory synapse number as well as postsynaptic differentiation of the dendrites [11–13]. In the developing cortex, MEF2C is the predominant isoform, and it is expressed in frontal and entorhinal cortex, cerebellum, dentate gyrus and amygdale [1,14,15].

In addition to gross motor delay and severely impaired expressive language, the majority of patients with *MEF2C* haploinsufficiency will present with seizures at some point in infancy (most commonly) or childhood. However, at this time, MEF2C-related epilepsy has not been well characterized with regard to the seizure semiology and EEG findings. Our patient has shown a variety of seizures types including febrile seizures, focal impaired awareness seizures, focal motor seizures with clonic manifestations, and generalized myoclonias. Autonomic features such as cutaneous pallor and hypopnea with cyanosis were also reported in our case. Data from previously reported patients also reinforce the broad spectrum of seizure types observed in MEF2C-related epilepsy, with febrile seizures being most common [1–10]. Along with the variability of seizure types are the EEG changes, with different epileptiform and non-epileptiform abnormalities.

Unfortunately, due to the small number of cases reported to date and a paucity of information regarding the epilepsy history, it is unclear whether patients with MEF2C haploinsufficiency will respond to antiepileptic medication or become medically refractory. Nor, is it known whether children with epilepsy and this genetic abnormality are more likely to respond to any specific monotherapy or combination of antiepileptic medications. Long term follow-up studies will be necessary to characterize to seizure outcome in these patients.

Despite having a relatively uniform clinical phenotype characterized by severely impaired expressive language, gross motor delay, stereotypies, and lack of typical facial dysmorphic features, patients with MEF2C-related epilepsy may present with a variety of different seizure types and electrographic findings. Pleiotropy is a very common characteristic of epilepsy genes, in which one gene is associated with different phenotypes, making the phenotype–genotype relationship complicated. In addition, the involvement of MEF2C in the transcriptional control (and decreased expression) of the *MECP2* and *CDKL5* genes [3], may also justify the variety of possible seizures in such patients.

5. Conclusion

Regardless of the lack of a unique seizure phenotype, this illustrative case and the literature review may allow us to delineate the MEF2C-related epilepsy as a spectrum including febrile seizures (typical or atypical), myoclonia, and focal onset or generalized seizures in the context of gross motor delay and severely impaired expressive language. EEG is consistently abnormal with a broad range of non-specific changes such as background slowing, multifocal and generalized epileptiform discharges as well as polyspikes (particularly prominent in our patient). Additional case identification may help to further expand and delineate our knowledge of the electro-clinical phenotype of

MEF2C-related epilepsy, including their response to specific treatments.

Conflict of interest statement

The authors declare no conflict of interests with respect to the authorship and publication of this article.

Authorship

All authors are eligible for author listing.

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