



Case Report

Valproic acid as a monotherapy in drug-resistant methyl-CpG-binding protein 2 gene (MECP2) duplication-related epilepsy

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ABSTRACT

Duplication of the methyl-CpG-binding protein 2 gene (MECP2) is a rare condition that results in epilepsy in half of the cases. Although this condition has been well characterized in the literature, there is a lack of research on MECP2 duplication-related epilepsy and its management.

We present the case of an eleven-year old male with MECP2 duplication and epilepsy, who was resistant to polytherapy. The patient responded well to valproic acid (VPA) initially and upon re-challenge. This case report provides evidence for the use of VPA as an initial monotherapy for treatment of drug-resistant MECP2 duplication-related epilepsy.

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1. Introduction

Duplications of Xq28 involving the methyl CpG binding protein 2 gene (MECP2) causes 0.5 to 2% of X-linked developmental disabilities and are predominantly inherited with full penetrance in males [1]. More severe mutations in MECP2 are lethal in males. Females with point mutations in MECP2 present with Rett syndrome. MECP2 duplication syndrome has been well-described in patients with mental retardation, absent to minimal speech, hypotonia replaced by progressive spasticity and/or ataxia, mild facial dysmorphisms (brachycephaly, large face, midface hypoplasia, depressed nasal bridge, upturned nares), severe recurrent respiratory infections, and in some cases, death before 25 years of age [2].

Approximately half of patients with MECP2 duplication also present with epilepsy, although this varies with age. Seizures generally develop in late childhood and early adolescence. Seizures present as polymorphic crises (absences, focal seizures, generalized tonic-clonic) or myoclonic or myoclonic-astatic forms with drop attacks [3]. The onset of seizures is thought to correlate with neurological deterioration including loss of speech and motor skills.

To date, there are 151 reported patients with MECP2 duplication syndrome, 87 of whom also have epilepsy. For a full summary of the

case studies and outcomes, see Table 1. Most of the cases described demonstrate that MECP2-related epilepsy is refractory to pharmacotherapy [4] or there was no reported response. In one case report [5], the patient responded to valproic acid initially, but seizures recurred after two years. Caumes et al. [4] reported seven patients on VPA, only one of which responded with complete control of atypical absence seizures at the 3-year follow-up. In another more recent study [6], two patients showed response with complete resolution of seizures with VPA in one case and a combination of VPA, Clobazam, and Lamotrigine in the other case. Limited research exists on patient attributes and epilepsy characteristics that make these patients responsive to therapy.

We describe an eleven-year old boy with MECP2-related epilepsy, who responded to VPA initially and upon re-challenge. This case provides evidence of the efficacy of VPA as a first-line monotherapy for treatment of MECP2 related epilepsy.

2. Case report

An eleven-year old boy was evaluated in the Neurology clinic. He was born at 39 weeks via emergency C-section in a pregnancy complicated by preeclampsia. Maternal history was significant for three prior miscarriages. There were no teratogen exposures during pregnancy. He was healthy with the exception of severe constipation as an infant. He had global developmental delays. He sat at 6 months, walked independently at 24 months, and was unable to ride a bike. He also had fine motor difficulties, particularly with writing letters and using

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Table 1
Previous studies of MECP2-related epilepsy.

First author (year)	Study	#of cases	Seizure types	Management	Outcome
Caumes (2014)	Late onset epileptic spasms is frequent in MECP2 gene duplication: electroclinical features and long-term follow-up of 8 epilepsy patients	8/8	Febrile seizures, complex partial, GTC myoclonic seizure	7/8 on VPA or combination of VPA with LTG/LVT/CLB/CBZ	6 refractory; 1 responsive to VPA
Vignoli (2012)	Electroclinical pattern on MECP2 duplication syndrome: eight new reported cases and review of literature	6/8	Atonic head drop, drop attacks, GTC, head nodding	6/6 on VPA or a combination of VPA with ETS/LEV/LTG/TPM	2 patients seizure free, 4 patients resistant
Bartsch (2010)	Four unrelated patients with Lubs X-linked mental retardation syndrome and different Xq28 duplications	2/4	Focal seizures, GTC	Anticonvulsants unknown	1 patient refractory, 1 patient responsive
Fernandez (2010)	Novel association of severe neonatal encephalopathy and Hirschsprung's disease in a male with a suplication at the Xq28 region	1/1	Focal seizures, GTC	N/A	N/A
Ramocki (2010)	The MECP2 duplication syndrome	9/14	GTC, focal seizure, eating reflex seizure	N/A	N/A
Reardon (2010)	Progressive cerebellar degenerative changes in the severe mental retardation syndrome caused by duplication of MECP2 and adjacent loci on Xq28	4/7	Drop attacks, nocturnal seizures, GTC	N/A	Refractory
Echenne (2009)	Neurological aspects of MECP2 gene duplication in male patients	3/5	GTC, myoclonic atstatic, atypical absence	VPA	Initially responsive, refractory after two years
Kirk (2009)	The clinical variability of the MECP2 duplication syndrome: description of two families with duplications excluding L1CAM and FLNA	2/3	N/A	N/A	N/A
Lugtenberg (2009)	Structural variation in Xq28: MECP2 duplication in 1% of patients with unexplained XLMR and in 2% of male patients with severe encephalopathy	7/13	Lennox–Gastaut syndrome, GTC, focal seizure	N/A	Refractory
Clayton-Smith (2008)	Xq28 duplication presenting with intestinal and bladder dysfunction and a distinctive facial appearance	8/16	Myoclonic seizures	N/A	N/A
Prescott (2008)	Two brothers with a microduplication including the MECP2 gene: rapid head growth in infancy and resolution of susceptibility to infection	1/2	N/A	Anticonvulsants, vagal nerve stimulator	N/A
Smyk (2007)	Different-sized duplications of Xq28, including MECP2, in the three males with mental retardation, absent, or delayed speech, and recurrent infections	1/3	GTCs	N/A	Deceased
Del Gaudio (2006)	Increased MECP2 gene copy number as the result of genomic duplication in male patients	1/7	N/A	N/A	N/A
Friez (2006)	Recurrent infections, hypotonia, and mental retardation caused by duplication of MECP2 and adjacent region in Xq28.	15/23	Atonic, focal seizure	N/A	Unknown
Van Esch (2005)	MECP2 duplication syndrome	4/9	GTC		Unknown
Meins (2005)	Submicroscopic duplication in Xq28 causes increased expression of the MECP2 gene in a boy with severe mental retardation and features of Rett syndrome	1/1	Absence, myoclonic atstatic seizures, GTCs	TPM/CLB/LTG/SUL	Refractory
Sanlaville (2005)	Functional disomy of the Xq28 chromosome region	5/13	N/A	N/A	N/A
Lubs (1999)	XLMR syndrome characterized by multiple respiratory infections, hypertelorism, severe CNS deterioration and early death localizes to distal Xq28	2/5	N/A	N/A	N/A
Pai (1997)	A new X linked recessive syndrome of mental retardation and mild dysmorphism maps to Xq28	4/6	N/A	N/A	Refractory
Lahn (1994)	Xq-Yq interchange resulting in supernormal X-linked gene expression in severely retarded males with 46, XYq-karyotype	3/3	Focal seizure, GTC	N/A	N/A
		Total	87/151		

utensils. From a language perspective, he was nonverbal and had deficits in receptive speech. His fourteen-year old brother had a genetic microarray confirming duplication of exons 3 and 4 MECP2 and triplication of exons 1 and 2 MECP2 and also had global developmental delay, absence of speech, and hypotonia. His younger brother and proband also had a duplication of MECP2 on testing. The patient's maternal grandmother had seizures and there was a history of epilepsy and cognitive impairment in other maternal relatives.

The patient presented with multiple dysmorphic features, including epicanthal folds, small palpebral fissures, long face, simplified helices, clinodactyly, small hands with poor capillary perfusion, and inverted nipples. He had mild scoliosis and kyphosis. His cranial nerve and motor exam were grossly normal. Reflexes were within normal limits. Cardiac auscultation revealed a systolic murmur at the left lower sternal border. He had a normal echocardiogram.

The patient presented with a history of seizures suggestive of focal dyscognitive seizures and generalized tonic–clonic seizures. The initial episodes were characterized by unresponsiveness, focal eye deviation, and post-ictal confusion with an unknown seizure

frequency. He also developed tonic–clonic episodes involving his four extremities. Later, he mainly had episodes of drop seizures, occurring 20–30 times daily and lasting minutes. As a result of these drop seizures, he lost his ability to walk independently and required significant assistance for his activities of daily living including eating, dressing, and bathing. He had several falls per week often resulting in soft tissue injuries. He was reported to have difficulty with concentration and executive functioning both at school and at home due to his uncontrolled seizures.

An initial MRI was normal and an EEG noted mild nonspecific slowing (7 to 8 Hz background frequency) with no obvious epileptiform activity. A genetics referral was made with requests for chromosomal microarray, Rett syndrome testing, CK, and a metabolic work-up. Genetic testing revealed a microduplication at Xq28 of 430 megabases, involving three genes: IRAK1, MECP2 and FLNA.

The patient was started on valproic acid (VPA) at 10 mL BID to be continued for two years. Since starting VPA, he was seizure-free. His brother, who was found to have the same MeCP2 duplication, also remained seizure free on VPA.

However, due to findings of thrombocytopenia and hyperbilirubinemia in the proband, the VPA was stopped. Following the discontinuation of VPA, he had a re-emergence of his epilepsy with an increase in his drop seizures. He was trialed on a multitude of other anticonvulsants, including Levetiracetam 1500 mg BID (9 months), Lamotrigine 150 mg BID (6 months), Oxcarbazepine 900 mg QAM–1200 mg QHS (4 months), Lacosamide 200 mg BID (3 months), Topiramate 150 mg BID (9 months), and Clobazam 10 mg QHS (ongoing) with no success. Given that the patient remained refractory to polytherapy and that the reported hyperbilirubinemia is a very rare occurrence, the VPA was re-started with close monitoring of transaminases and bilirubin levels. Laboratory studies showed a normalization of platelets and bilirubin levels.

Upon re-challenge, his convulsive seizures were controlled with a significant decrease in frequency of his drop attacks occurring 1–2 times daily. Initially he would have 20–30 drop seizures each day accompanied with unresponsiveness, greatly affecting his ability to function. However, with the reduction in seizure activity, his activities of daily living and school performance improved markedly. In addition, as per parent report, the removal of the sedating anticonvulsants made him less drowsy. Overall, his improved functioning translated in reduced caregiver stress and better quality of life for the patient.

3. Discussion

This case study describes a patient with MECP2-related epilepsy who had an initial favorable response to valproic acid (VPA), followed by discontinuation of therapy and re-emergence of symptoms despite polytherapy, and subsequently a re-challenge of VPA which achieved seizure control. This study provides unique evidence for the efficacy of VPA as an initial monotherapy in MECP2 duplication-related epilepsy.

The majority of previous cases of MECP2 duplication-related epilepsy in the literature have shown poor response to therapy or drug resistance. In one case series [6], two patients had complete seizure control following treatment. For both of these patients from the literature, VPA was part of the treatment regimen. The first patient developed epilepsy at the age of twelve years with atonic head drop and generalized tonic-clonic seizures with EEG showing irregular background activity. Valproic acid was started with complete seizure control. The second patient started having seizures at thirteen years of age. His episodes initially presented as drop attacks with an EEG showing rhythmic theta activity over the frontal areas and paroxysmal spike and slow waves and fronto-temporal predominance. The seizures were initially responsive to a polytherapy with VPA, Clobazam, and ethosuximide, but later re-emerged. Following the addition of Lamotrigine and removal of ethosuximide, the patient achieved complete seizure control. An additional patient also responded to VPA [4] and had a background of predominantly absence seizures.

The current case and the two previously documented reports demonstrate that seizure activity in MECP2 duplication syndrome can be responsive to VPA. The mechanism of action of VPA is not fully understood, but it is thought to act via multiple pathways including blockage of voltage-gated sodium channels and increased levels of gamma-aminobutyric acid (GABA) [7]. This generalized mechanism makes VPA an ideal initial antiepileptic in MECP2-duplication related epilepsy.

It is unknown as to which factors differentiate patients who were refractory to treatment versus those who responded to VPA. The difference may reflect varying genetic modifiers modulating the complex epileptic networks. Limited research exists on the polygene impact of IRAK1, MECP2 and FLNA. Fukushi et al. [8] identified one family with a similar combination of genes, who displayed hypotonia, severe intellectual disability and developmental delay, lack of speech, mild characteristic facial features, pyramidal signs, untreatable epilepsy, regression, recurrent infections, and mortality before they were 25 years old. However, these individuals had a duplication which also included the L1CAM

gene. To date, the specific contribution of IRAK1 is not well-delineated, but may modulate immune responses. FLNA duplications have been shown to be related to bowel dysfunction including constipation, which was identified in this patient [9].

All responders, including the patient under discussion, developed late-onset epilepsy occurring after the first year of life, with three of the patients developing seizures in early adolescence. The types of seizures in the responsive patients may also be different from those of the non-responders. In the previous studies, one treatment responder displayed atypical absence seizures exclusively [4] and the other two demonstrated atonic head drops and drop attacks respectively [6]. Our patient also predominantly had drop attacks as compared to other seizure types. This is in contrast to the many non-responders who had seizures of multiple types resembling Lennox–Gestalt syndrome. There were additionally similar electroclinical signatures in the responsive patients with unusual fast rhythmic activities occurring in addition to the slow background activity. These observations, however, require further study in a larger patient sample.

Nevertheless, the underlying seizure types that occur in MECP2-related epilepsy are well-suited to the generalized effects of VPA. Previous cases of MECP2 duplication syndrome demonstrate that seizures are often polymorphic occurring frequently in the form of generalized tonic-clonic, atypical absence, atonic, and myoclonic seizures [6]. As such, an antiepileptic drug with a broad spectrum of activity is a good initial consideration. The Standard and New Antiepileptic Drugs (SANAD) trial identified VPA as the first-line treatment for patients with generalized seizures [10].

Further, the EEG features associated with MECP2 duplication related epilepsy mimic a generalized pattern of activity. Specifically, in the documented cases, the interictal EEG showed a slowing of the background activity with generalized slow spike and wave asynchronous discharge with frontotemporal predominance. Sleep EEG also shows abnormal background activity with high voltage spindles [6]. This EEG pattern closely reflects activity present in myoclonic seizures and genetic generalized epilepsy syndromes. Given the widespread nature of cortical activity, VPA is a good choice due to its multiple mechanisms of action.

VPA is also a possible option in MECP2 duplication syndrome as a majority of patients are males and do not have the added risk of pregnancy-related complications including teratogenicity. Current evidence states that VPA is the first-choice treatment option in males and post-menopausal women, while it is not recommended for use in women of child-bearing age and patients with obesity [10]. In these contraindicated cases, Lamotrigine can be used as an alternative agent. Lamotrigine is a phenyltriazine derivative that has a similar mechanism of action to that of VPA in that it inhibits voltage-activated sodium channels. As discussed, in a patient previously reported in the literature who responded to a combination of VPA and Lamotrigine, Lamotrigine served to augment the efficacy of VPA in controlling generalized seizures. This represents an additional reason for starting on VPA as an initial monotherapy as it can be combined with Lamotrigine in the case of treatment resistance [11].

Despite the fact that VPA is the most effective monotherapy with lower treatment withdrawal in generalized epilepsy, the adverse event and side effect profile must be taken into consideration. VPA has multiple side effects including weight gain, hair loss, and gynecomastia [12]. In the current case, there was the additional issue of thrombocytopenia, which is a well-described hematological side effect of VPA. However, thrombocytopenia alone is not an indication to discontinue treatment, and recent evidence suggests that a reduction in dose with strict laboratory controls can be sufficient to normalize patient values [13]. Furthermore, while hepatotoxicity is common, there are no reported cases of hyperbilirubinemia in VPA, suggesting that this finding in our patient was either incidental or due to an unrelated etiology. As such, the patient was appropriately re-trialed on VPA with reduction of the dosage and close monitoring of platelets and transaminases.

4. Conclusion

To our knowledge, this is the first reported case of drug-resistant MECP2 duplication related epilepsy, showing responsiveness to VPA both initially and upon a re-challenge, strongly supporting the efficacy of this anticonvulsant as a monotherapy. The case highlights the benefits of VPA in targeting the generalized seizure types and EEG activity seen in MECP2 duplication syndrome. It also suggests that side effects of VPA such as thrombocytopenia can be mitigated by a dose reduction and re-challenge with close monitoring of laboratory markers. Although most cases in the literature suggest that epilepsy associated with MECP2 duplication syndrome is treatment-resistant, we provide contrasting evidence that there may be a role for VPA as a monotherapy in achieving seizure control in some patients.

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