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Case Report

Migrating partial seizures in infancy and 47XYY syndrome: Cause or coincidence?

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ABSTRACT

Migrating partial seizures in infancy (MPSI) is a rare epilepsy syndrome with poor prognosis. The exact etiology of MPSI is still not known. We report a 14-month-old baby with 47XYY karyotype who presented with developmental delay and drug-refractory seizures satisfying the diagnostic criteria for MPSI and discuss the possible association between the 47XYY karyotype and this syndrome. The excess of genes due to an additional Y chromosome could cause disturbance in various stages of formation, migration, or differentiation of neurons. Depending on the degree of disturbance and the resultant cortical excitability, this could result in various epilepsy syndromes. We feel that this association is more likely causal than coincidental. Chromosome studies need to be performed in more individuals with atypical and uncommon epilepsies. Multicenter studies are required to establish the association between epilepsy syndrome and these rare chromosome disorders.

1. Introduction

Migrating partial seizures in infancy (MPSI), earlier known as malignant migrating partial seizures in infancy, is a very rarely reported epilepsy syndrome with unknown etiology. This report describes a child with 47XYY karyotype who presented with clinical features of MPSI and discusses the possible nature of an association between this catastrophic epilepsy syndrome and the excess Y chromosome.

2. Case report

A 14-month-old boy presented with developmental delay and refractory seizures from the age of 5 months. He was the only child born to a nonconsanguineous couple. Family history was insignificant. His perinatal period had been uneventful. He had developed a social smile by the age of 8–10 weeks, and he was able to hold his head up by the age of 4 months. He started getting seizures at the end of the fifth month. At the end of the fifth month, he started having seizures. Seizures were associated with head deviation to either side along with tonic posturing of arms and legs of either side. These events would last 1–2 min. The initial frequency was 2–3 per day, but, gradually, over the next 3–4 months, it increased to 10–20 per day. At present, he gets around 30–40 per day. His seizures had failed to improve with various antiepileptic drugs. He had lost all and did not gain any new developmental milestones.

Examination revealed a head circumference of 41 cm (<2 SD). There were no neurocutaneous markers or dysmorphic features. Reduced interaction and alertness were found in the child. There was floppiness on lifting the child, otherwise neurological and systemic examination was unremarkable. Magnetic resonance imaging of the brain did not reveal any abnormalities. Detailed evaluation including urine ketones, plasma acylcarnitine profile, urine gas chromatography–mass spectrometry for organic acids, arterial blood gas, blood lactate and ammonia levels, hair microscopy, serum copper and ceruloplasmin levels, thyroid profile, and cerebrospinal fluid evaluation was normal.

A video-EEG evaluation showed few focal seizures involving the right half of the body (Video 1) and the remaining few involving the left half of the body (Video 2). The corresponding ictal EEG showed seizure origin from the left hemisphere (Fig. 1d) and from the right hemisphere (Fig. 1c). The interictal EEG showed multifocal spikes (Fig. 1a) and burst-attenuation pattern (Fig. 1b). Karyotyping revealed a supermale with 47XYY pattern (Fig. 2).

3. Discussion

3.1. Diagnostic criteria of MPSI

The diagnostic criteria of MPSI include 1) the presence of normal development before seizure onset, 2) onset of seizures before

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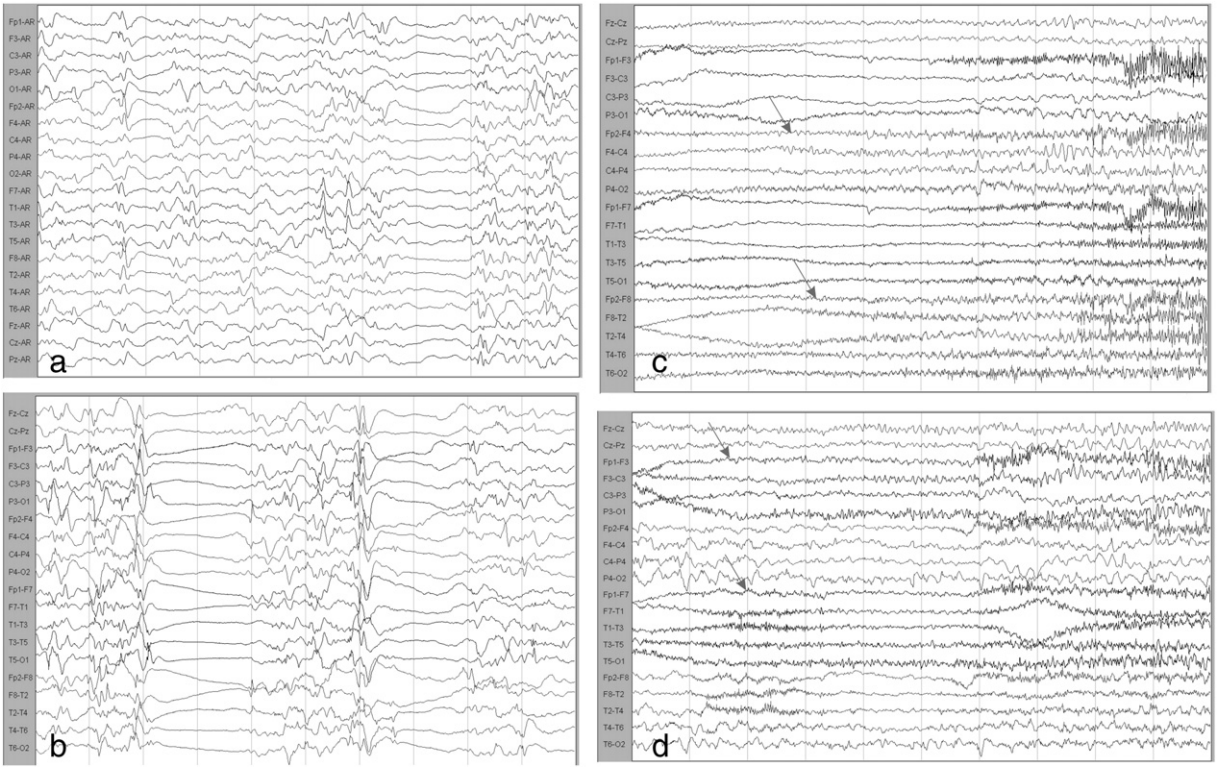

Fig. 1. Interictal EEG showing multifocal spikes (a) and burst-attenuation pattern (b). Ictal EEG showing right hemispheric seizure onset (arrows) with fast activity noted over the right hemisphere best expressed over the posterior leads (c) and left hemispheric seizure onset (arrows) with fast activity noted over the left hemisphere best expressed over the posterior leads (d).

6 months, 3) migrating focal motor seizures at onset, 4) multifocal seizures becoming intractable, 5) seizures intractable to conventional antiepileptic drugs, 6) no identified etiology, and 7) profound psychomotor delay [1]. Our case satisfies all the criteria for the diagnosis of MPSI. Interestingly, the child turned out to be a supermale with XYY genotype.

3.2. Etiology of MPSI: available data

The exact etiology of MPSI is still not known. However, the age-dependent seizure onset, the multifocal nature of seizures and interictal discharges, and the decline of head circumference with age could suggest a metabolic disease, a channelopathy, or a genetic disorder, though

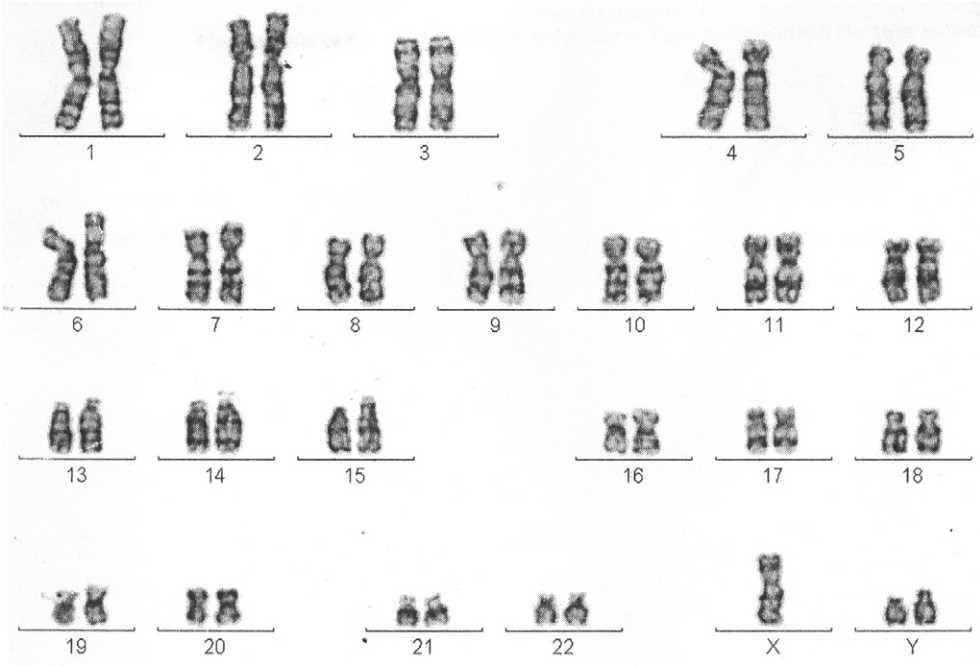

Fig. 2. Chromosome preparation showing an additional Y chromosome.

none have been identified so far. No abnormalities in the coding region of important sodium, potassium, and chloride ion channels could be identified in one study [2]. Similarly, postmortem studies in patients with MPSI have not revealed any significant structural abnormalities [3–6]. Search for the genetic basis of MPSI has also not yielded any major results so far. Though isolated instances of certain abnormalities like 16p11.2 microduplication [7], *SCN1A* missense mutation, and deletion encompassing the entire *SCN1A* gene and other sodium channel subunit genes [8] occurred, their causal association with MPSI could not be established. A familial form of MPSI due to mutation in TBC1D24 was described recently in two affected siblings [9]. A de novo gain-of-function mutation in the C-terminal domain of the KCNT1 potassium channel was identified in 6 out of 12 unrelated patients with MPSI [10]. An inherited homozygous deletion of the gene phospholipase C beta 1(PLCB1) was also identified in another child with MPSI [11]. These data point towards a genetic heterogeneity in MPSI [12].

3.3. Chromosomal anomalies and epilepsy

Chromosomal anomalies, either structural or numerical, are very commonly associated with epilepsy [13]. Many autosomal disorders like Miller–Dieker syndrome, Angelman syndrome, and ring chromosome 14 and 20 syndromes have a high association with epilepsy. When it comes to sex chromosomes, X chromosome anomalies have been well described to be associated with epilepsy. This includes Fragile X syndrome [14], Klinefelter's syndrome [15], X chromosome aberrations, and triple X syndrome [16]. The X chromosome in comparison with the Y chromosome is rich in genes and has the highest frequency of mutations and microdeletions associated with neurogenetic disorders [17].

3.4. 47XYY karyotype and epilepsy

47XYY karyotype is a Y chromosome aneuploidy characterized by an extra copy of the Y chromosome with an incidence of 1/1000 males. Volavka et al. [18] reported lower frequency of background alpha in XYY patients and suggested that extra Y chromosome interferes with normal brain functioning. Macleod et al. [19] reported 2 patients with XYY syndrome and epilepsy; one developed flexor spasms at eight months and hypsarrythmia in the EEG while the second one developed complex partial seizures from five years of age, and the interictal EEG showed multifocal spike complexes. Torniero et al. [20], in their analysis of four patients, described that benign childhood epilepsy with centrotemporal spikes (BECTS) like electroclinical pattern correlated to 47XYY karyotype.

3.5. The possibilities in our case

We, thus, report a boy with a 47XYY karyotype and infantile refractory seizures satisfying the diagnostic criteria for MPSI. To our knowledge, this clinical association between MPSI and 47XYY karyotype is not yet reported. Whether this association is causal or just a coincidence is uncertain. The “triplo-excess” of genes in 47XYY karyotype could be expected to cause disturbance in various stages of formation, migration, or differentiation of neurons [13]. The extent of this disturbance and the associated cortical excitability could determine the epilepsy syndrome in the patient. This could range from BECTS with very focal disturbance progressing through symptomatic localization-related epilepsy syndromes with complex partial seizures, MPSI with more diffuse and bilateral cortical excitability, and symptomatic generalized epilepsy syndromes like West syndrome with very extensive cortical dysfunction.

4. Conclusion

We consider this association between MPSI and 47XYY karyotype as probably causal rather than coincidental. However, one report is insufficient, and further observations are necessary to establish this association. Chromosome studies need to be performed in more individuals with atypical and uncommon epilepsies and also in situations where the etiology is uncertain. Considering the rarity of chromosomal disorders, multicenter studies are also required to establish the association between epilepsy syndrome and chromosomal disorders. This association of MPSI with an excess copy of Y chromosome, if established, could not only strengthen the hitherto weak link between Y chromosomal disorders and epilepsy but also give clues to gene hunters looking for epileptogenic regions on chromosomes. Our observation of this association may aid the ongoing research to unravel the exact mechanism underlying this devastating epilepsy syndrome which could translate into more effective clinical interventions.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ebcr.2014.02.003.

Conflict of interest

There are no conflicts of interest.

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