


# Trisomy 8 Mosaicism and Favorable Outcome After Treatment of Infantile Spasms: Case Report

Journal of Child Neurology  
25(10) 1275-1277  
© The Author(s) 2010  
Reprints and permission:  
sagepub.com/journalsPermissions.nav  
DOI: 10.1177/0883073809357361  
http://jcn.sagepub.com  


Anita Datta, MD, FRCPC,<sup>1</sup> Jonathan Picker, MD, PhD,<sup>2</sup> and Alexander Rotenberg, MD, PhD<sup>1</sup>

## Abstract

Constitutional mosaic trisomy 8 syndrome occurs in approximately 1 of 35 000 live births. Clinically, it has a variable presentation. Some patients are asymptomatic, while others have multisystemic involvement. The overall incidence of neurological abnormalities has not been reported, but seizures are among the neurological symptoms associated with this condition. Previous reports describe astatic seizures, complex partial seizures, generalized tonic-clonic seizures, and absence seizures with the age of onset varying from 3 months to early childhood. However, instances of infantile spasms and the patients' response to treatment have not been reported to our knowledge. Accordingly, we report a case of a patient with constitutional mosaic trisomy 8 syndrome and infantile spasms, who became seizure free after treatment with adrenocorticotrophic hormone and clonazepam.

## Keywords

infantile spasms, trisomy 8 mosaicism, Warkany syndrome

Received July 23, 2009. Accepted for publication November 17, 2009.

Constitutional mosaic trisomy 8 syndrome, also known as Warkany syndrome, is one of the most common autosomal trisomies after chromosomes 21, 18, and 13, occurring in live-born individuals with an incidence of approximately 1 of 35 000 live births.<sup>1</sup> The male to female ratio is 5:1.<sup>2</sup> Constitutional mosaic trisomy 8 syndrome is only compatible with survival in the mosaic form.<sup>3-5</sup> Clinical features are quite variable with multiple systemic and neurological phenotypes. Among the systemic abnormalities of constitutional mosaic trisomy 8 syndrome are dysmorphic facies, cleft palate, congenital heart malformations, renal malformations, and musculoskeletal anomalies.<sup>3,6,7</sup>

Although central nervous system abnormalities such as seizures and mental retardation are often described, the relationship of constitutional mosaic trisomy 8 syndrome and seizures is poorly defined. Notably, to our knowledge, infantile spasms have not been previously published in a child with constitutional mosaic trisomy 8 syndrome. Accordingly, we report a case of a patient with constitutional mosaic trisomy 8 syndrome and infantile spasms, who responded favorably to treatment with adrenocorticotrophic hormone (ACTH) and clonazepam.

## Methods

The details of the case and related diagnostics were reviewed by the authors. Additionally, after a PubMed search using keywords "trisomy 8 mosaicism," "infantile spasms," "seizures," "trisomy 8," and

"C-group trisomies" from 1971 to the present, we reviewed all identified papers and, where relevant, contacted the corresponding author for details and clarification.

## Case

At presentation, the patient was a 17-month-old white male referred for evaluation of head drops noticed by the parents at 8 months of age. Until that age, his development had been normal. He was otherwise in good health. The concerning symptoms were characterized by the head falling toward the chest and the patient falling from a sitting position with a nearly immediate recovery. The drops occurred in clusters of 7 to 10 events at a rate of 1 to 3 clusters per day. He did not have any developmental regression with the onset of the spasms.

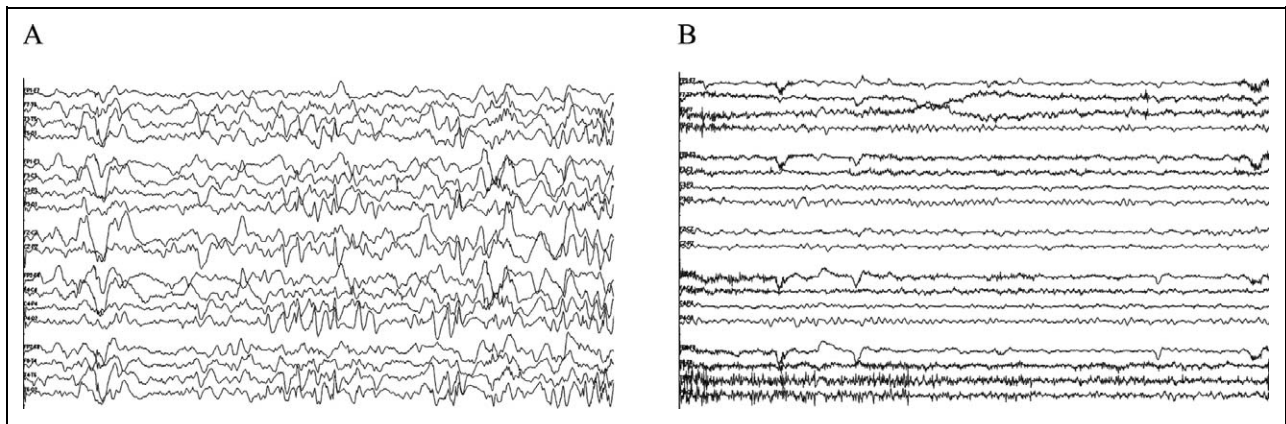
<sup>1</sup> Division of Epilepsy, Department of Neurology, Children's Hospital Boston, Boston, Massachusetts

<sup>2</sup> Division of Genetics, Department of Medicine, Children's Hospital Boston, Boston, Massachusetts

## Corresponding Author:

Alexander Rotenberg, Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Children's Hospital, Harvard Medical School, 300 Longwood Avenue, Boston, MA 02115

Email: alexander.rotenberg@childrens.harvard.edu



**Figure 1.** (A) Representative electroencephalography (EEG) before treatment. The 10-second tracing shows a background with irregular slowing along with multifocal spikes and sharp waves characteristic of hypsarrhythmia before treatment with adrenocorticotrophic hormone (ACTH). (B) Representative EEG after treatment. Following treatment, the awake EEG shows a normal background pattern, without epileptiform features.

The patient had been born to a 35-year-old gravida 7 para 2 mother. Four prior pregnancies were spontaneous abortions in the first trimester. The mother's pregnancy was complicated by hypertension but otherwise unremarkable. He was delivered at 38 weeks' gestation with a birth weight of 8 lb and 4 oz by caesarian section. His perinatal course was uneventful.

His parents were nonconsanguineous. Both parents and 2 sisters, 8 and 6 years of age, were in good health. A cousin on the patient's father's side had autism. Otherwise, family history was unremarkable with no history of mental retardation, learning defects, birth defects, or genetic syndromes. On physical examination, he was interactive with his environment. His height was 80.3 cm (25th percentile-50th percentile), weight was 10.7 kg (90th percentile), and head circumference was 46 cm (25th percentile). His eyes had mild epicanthal folds. There was a linear crease running down from the second toe area bilaterally, as is characteristically seen in constitutional mosaic trisomy 8 syndrome. Otherwise, there were no other dysmorphic features. The remaining results of his systemic examination and his neurological examination were normal.

He had several investigations to determine the etiology of his spasms, including brain magnetic resonance imaging and metabolic and Wood lamp tests, the findings of which were normal. Genetic testing revealed constitutional mosaic trisomy 8 syndrome, specifically 46, XY,+8(3); 46, XY(17). He also had a duplication of 8q24.3, thought unlikely to be pathological given identical and asymptomatic duplication in the boy's father.

Video electroencephalography (EEG) monitoring showed hypsarrhythmia with a high amplitude disorganized background with multifocal spikes and sharp waves (Figure 1A). The clinical spasms corresponded with high voltage polyspike and slow-wave bursts followed by a generalized attenuation, a pattern consistent with infantile spasms. Treatment with ACTH (150 U/m<sup>2</sup>) was started promptly after diagnosis. Within 1 week, he had a reduction in spasm frequency with a course of ACTH, but this was short lived, and spasms resumed at baseline frequency after 4 weeks. He was then started on

clonazepam 0.125 mg in the morning and 0.25 mg at night without side effects. Two weeks later, there was a cessation in spasms. His repeat EEG results (Figure 1B), 4 months after diagnosis, were normal for his age.

On follow-up, 8 months later, he remained seizure free. Clonazepam was weaned over 3 months uneventfully. At the time of this writing, the patient is 26 months of age, remains without seizures, and is not on any antiepileptic medications. In follow-up, after seizure resolution, he had normal motor development for his age; however, he had prominent language delay with a vocabulary of 3 to 4 single words and no ability to put words together in phrases. He is enrolled in the early intervention developmental services.

## Discussion

The present report is a case of a patient with constitutional mosaic trisomy 8 syndrome, who presented with infantile spasms at 8 months of age and had complete resolution of his symptoms after a course of ACTH followed by treatment with clonazepam.

Constitutional mosaic trisomy 8 syndrome is likely underdiagnosed due to a highly variable phenotypic expression. Some patients are asymptomatic, while others have multisystemic involvement. The wide clinical variability is likely due to the degree of mosaicism as well as different break points within the 8p23.1 region and tissue-specific mosaicism.<sup>8,9</sup> The genetic heterogeneity was shown in a molecular study on constitutional mosaic trisomy 8 syndrome using 26 subjects and 19 micro-satellite markers. Twenty of the cases were due to postzygotic duplication. Two cases were due to maternal meiotic nondisjunction, presumably with chromosomal rescue; in 4 cases, it was not possible to detect the trisomy due to low levels of mosaicism.<sup>10</sup>

Neurological features of constitutional mosaic trisomy 8 syndrome include agenesis of the corpus callosum, mild to moderate mental retardation, and a predisposition to language delay.<sup>4,7,11</sup> The association of constitutional mosaic trisomy 8 syndrome and seizures is poorly defined. Notably, our review of the literature

did not reveal any report of infantile spasms in the constitutional mosaic trisomy 8 syndrome neurological phenotype.

Seizures have been described in chromosomal aberrations involving the distal part of chromosome 8 and 8q24 in particular.<sup>10</sup> Deletions of 8q24 can lead to syndromes with frequent seizures, such as Langer-Giedion syndrome characterized by mild to moderate learning difficulties, short stature, unique facial features, small head, and skeletal abnormalities including bony growths projecting from the surfaces of bones.<sup>12</sup> It is proposed that candidate genes at 8q24 might be responsible for the epileptic phenotype in a dosage-sensitive manner.<sup>9</sup>

Astatic seizures, complex partial seizures, generalized tonic-clonic seizures, and absence seizures have been previously reported with age of onset varying from 3 months to early childhood.<sup>11,13,14</sup> One report describes a patient with epilepsy, who was diagnosed with constitutional mosaic trisomy 8 syndrome in adulthood but who reportedly had seizure onset in infancy.<sup>15</sup> Published data suggest a variable response to antiepileptic medications. In one reported case, zonisamide was effective for astatic and generalized seizures but not for complex partial seizures, which was refractory to zonisamide, clonazepam, and carbamazepine.<sup>13</sup> In another case, carbamazepine was used for generalized seizures, but these continued after treatment.<sup>11</sup>

Our literature search did not identify any other reported constitutional mosaic trisomy 8 syndrome cases of infantile spasms with hypsarrhythmia. Infantile spasms are an age-related seizure type that is typically refractory to conventional anticonvulsant medications. As ACTH (along with corticosteroids and vigabatrin) is among the most common first-line treatment for infantile spasms, we chose this agent as the initial therapy.

The overall neurological prognosis after infantile spasms is generally determined by the underlying pathological process and often is characterized by epilepsy and developmental delay. When developmental delay or developmental regression accompanies infantile spasms, the term “West syndrome” is applicable and appropriate in the present case. In as many as half of the patients with infantile spasms, seizures persist into later childhood as Lennox-Gastaut syndrome, a childhood epileptic encephalopathy characterized by multiple seizure types and slow spike and wave on EEG.<sup>16</sup>

There is currently a paucity of literature on the description of seizures and constitutional mosaic trisomy 8 syndrome. The reported patient with infantile spasms had a favorable response to a course of ACTH followed by clonazepam monotherapy. This suggests that infantile spasms in this population may be controlled with a conventional regimen, although certainly more data are required to better characterize infantile spasms in constitutional mosaic trisomy 8 syndrome and their response to treatment.

### Acknowledgments

All work was performed at Children’s Hospital Boston.

### Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

### Funding

The authors received no financial support for the research and/or authorship of this article.

### References

- Nielsen J, Wohler M. Chromosome abnormalities found among 34,910 newborn children: results from a 13 incidence study in Arhus, Denmark. *Human Genetics*. 1991;93:243-247.
- Karadima G, Bugge M, Nicolaidis P, et al. Origin of nondisjunction in trisomy 8 and trisomy 8 mosaicism. *Eur J Hum Genet*. 1998;6:432-438.
- Miller K, Arsian-Kirchner A, Schulze, B, et al. Mosaicism in trisomy 8: phenotype differences according to tissular repartition of normal and trisomic clones. *Ann Genet*. 1997;40:181-184.
- Bonaglia MC, Giorda R, Tenconi R, et al. A 2.3 Mb duplication of chromosome 8q24.3 associated with severe mental retardation and epilepsy detected by standard karyotype. *Eur J Hum Genet*. 2005;13:586-591.
- Yamanouchi H, Imataka G, Nakagawa E, et al. An analysis of epilepsy with chromosomal abnormalities. *Brain Dev*. 2005;27:370-377.
- Felbor U, Knotgen N, Schams G, et al. Mosaicism for an ectopic NOR at 8pter and a complex rearrangement of chromosome 8 in a patient with severe psychomotor retardation. *Cytogenet Genome Res*. 2004;106:55-60.
- Hrachovy RA, Gospe SM, Glaze DG. High-dose, long duration versus low-dose, short-duration corticotrophin therapy for infantile spasms. *J Pediatr*. 1994;124:803-806.
- Gorlin RJ, Cohen MM, Levin LS. Chromosomal syndromes: common or well-known syndromes. In: *Syndromes of the Head and Neck*. 3rd ed. New York: Oxford University Press; 1990:49-50.
- Kurtyka ZE, Krykwa B, Piatkowska E, et al. Trisomy 8 mosaicism syndrome: two cases demonstrating variability in phenotypes. *Clin Pediatr*. 1988;27:557-564.
- Schnizel A. *Catalogue of Unbalanced Chromosome Aberrations in Man*. 2nd ed. New York: Walter de Gruyter; 2001.
- De Grouchy J, Turleau C, Leonard C. Study by fluorescence of a trisomy C mosaic, probably 8:46, XY,78+. *Ann Genet*. 1971;14:69-72.
- Wisniewska M, Mazurek M. Trisomy 8 mosaicism syndrome. *J Appl Genet*. 2002;43:115-118.
- Serur D, Jeret JS, Wisniewski K. Agenesis of the corpus callosum: clinical, neuroradiological and cytogenetic studies. *Neuropediatrics*. 1988;19:87-91.
- Beighton P, Kozlowski KS, Gardner J, et al. Broad clavicles in trisomy 8 mosaicism: a new sign. *Skeletal Radiol*. 1999;28:359-361.
- Helbig I, Wirtenberger M, Jauch A, et al. Trisomy 8q and partial trisomy 22 in a 43-year-old man with moderate intellectual disability, epilepsy and large cell non-Hodgkin lymphoma. *Am J Med Genet*. 2006;140:1658-1662.
- Matsumoto A, Watanabe K, Negoro T, et al. Long-term prognosis after infantile spasms: a statistical study of prognostic factors in 200 cases. *Dev Med Child Neurol*. 1981;23:51-65.