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FULL-LENGTH ORIGINAL RESEARCH

Spectrum of epilepsy in terminal 1p36 deletion syndrome

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SUMMARY

Purpose: Previous reports have summarized the seizures types occurring in 1p36 deletion syndrome. To better define the spectrum of epilepsy, we studied 91 patients (median age 7.8 years) with confirmed 1p36 deletion.

Methods: Based on clinical charts, we retrospectively analyzed the evolution of both the EEG findings and seizures.

Results: Epilepsy occurred in 53 patients (58.2%), with onset at a median 2.75 months. First seizures were generalized tonic (8 cases), tonic and clonic (6) or myoclonic (12), simple partial (6), or complex partial (14). Thereafter, 20 patients (21.9%) developed infantile spasms with hypsarrhythmia, at a median age of 5 months. High doses of oral steroids were tried in nine cases, with a prompt remission of seizures in six. Among them, five were seizure-free at the time of evaluation. Conversely, two of three nonresponders to steroids developed severe and refractory epilepsy.

At the time of evaluation, 32 patients were seizure-free, from a median age of 1.8 years. Nineteen patients (20.9%) had developed refractory epilepsy with polymorphic seizures, including generalized tonic and tonic–clonic seizures (13) combined with myoclonic seizures (11) and atypical absences (3), atonic seizures (2), or complex partial seizures (3). The EEG showed focal, multifocal or generalized spikes, polyspike, and waves, with poverty of the usual background rhythmic activities.

Conclusions: Early epilepsy is a frequent finding in 1p36 deletion syndrome with infantile spasms as of the most common features that can contribute to a poor clinical outcome. Early diagnosis and management of infantile spasm in this condition is mandatory.

KEY WORDS: Monosomy, Deletion, 1p36 syndrome, Epilepsy, Infantile spasms.

Epilepsy and mental retardation are frequently found in chromosomal abnormalities syndromes. In such syndromes, epilepsy is challenging since it occurs in the context of a preexisting handicap. In addition, when chromosomal abnormalities are associated with epileptic encephalopathy such as infantile spasms, long-term cognitive outcome can seriously be impaired (Battaglia & Guerrini, 2005; Parmeggiani et al., 2005). For these reasons, clinicians make strong efforts to make the most accurate characterization of epilepsy syndrome in chromosomal

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abnormalities. Indeed, better analysis of epilepsy phenotype not only leads to improved management of patients but also aid to its diagnosis. Among chromosomal abnormalities, distinct epileptic phenotypes are characterized by myoclonic/atonic seizures and atypical absences in Angelman syndrome (Minassian et al., 1998), clonic and tonic–clonic seizures, followed by atypical absences with mild myoclonic jerks in Wolf–Hirschhorn syndrome (Battaglia et al., 2003; Battaglia & Guerrini, 2005; Kagitani-Shimono et al., 2005), or Lennox–Gastaut syndrome in Inv-dup 15 (Battaglia et al., 1997; Battaglia & Guerrini, 2005). Infantile spasms are occasionally observed in Inv-dup15 (Bingham et al., 1996) and are commonly associated with trisomy 21 (Pueschel et al., 1991; Silva et al., 1996).

Terminal deletion 1p36 (Del 1p36) is a newly recognized syndrome with multiple congenital anomalies and mental retardation (Shapira et al., 1997; Slavotinek et al., 1999; Shaffer & Heilstedt, 2001; Battaglia, 2005). For individuals with Del 1p36 syndrome, moderate to severe mental retardation, characteristic cranio-facial features, hypotonia are almost universally observed (Battaglia, 2005). Gross motor skills as well as language are also significantly impaired. Additional common findings are epilepsy, cardiac defects, hearing loss, hypothyroidism, and midline defects (Shapira et al., 1997; Slavotinek et al., 1999; Shaffer & Heilstedt, 2001). Maternally derived de novo deletions are significantly more frequent than paternally derived deletions. The deletion size varies in each family, possibly providing phenotypic variability as a result of haploinsufficiency of different genes (Heilstedt et al., 1999; Wu et al., 1999).

Although Del 1p36 is now considered the most common terminal deletion syndrome with an estimated incidence of 1 in 5,000 (Shaffer & Heilstedt, 2001), there is very limited published data on the epileptic phenotype, on EEG findings, and on the natural history of epilepsy in Del 1p36 syndrome. In the literature, seizures do occur in 50% of the patients (Heilstedt et al., 2003b) and are of different types, including infantile spasms, simple or complex partial, generalized tonic–clonic, myoclonic, and absence seizures (Reish et al., 1995; Giraudeau et al., 1997; Shapira et al., 1997; Riegel et al., 1999; Slavotinek et al., 1999). Age of onset is difficult to retrieve from the literature since most reports do not specify it. However, from the available data, it seems as if seizures occur during infancy or childhood and control of seizures with current antiepileptic drugs is variable (Heilstedt et al., 1999; Slavotinek et al., 1999; Kurosawa et al., 2005). EEG abnormalities vary greatly and include hypsarhythmia, focal and multifocal spikes, and asymmetry of slow wave activity (Knight-Jones et al., 2000; Battaglia, 2005)

In the present paper, we describe the electroclinical features of 91 patients with Del 1p36 syndrome, in order to obtain better information on the characteristics of epilepsy, including seizures semiology and EEG features, and on its natural history. To our knowledge, this study is the largest report on a detailed analysis of the electroclinical characteristics of epilepsy in this syndrome.

Patients and Methods

We retrospectively studied the electroclinical pattern of 91 patients diagnosed with 1p36 deletion. There were 64 females and 27 males. The median age at the final visit was 7.8 years (from 1 to 25 years). Eighty out of the 91 patients (87.9%) had a pure 1p36 deletion, whereas the other 11 (12.1%) had a more complex rearrangement.

Clinical details were obtained by direct interview to the parents and review of medical histories, after gaining informed consent from parents. All patients received a careful physical and neurological evaluation.

The hospital files were retrospectively reviewed to determine seizure history and classification, with specific attention to seizure incidence, types and frequency, and response to treatment. Epilepsies were classified according to the 1989 recommendations of the International League Against Epilepsy (ILAE 89).

Polygraphic video-EEG recordings were carried out while patients were awake and asleep at 15 or 30 mm/s on paper, with a 10- or 20-channel EEG apparatus (10–20 system) with bipolar and referential montages using silver–silver chloride surface electrodes, at the onset of epilepsy and during its course. The results of routine EEG studies performed in other institutions were obtained by chart review.

This study was approved by the research ethics committee of the different Hospital (Necker Enfants Malades, Paris; Pitié Salpêtrière, Paris, Robert Debré, Paris; Hôpital Trousseau, Paris, Pellegrin-Enfants, Bordeaux, Lyon Sud, Lyon, France; Stella Maris Clinical Research Institute for Child and Adolescent Neuropsychiatry, Pisa, Italy).

Results

Clinical findings

All patients showed characteristic craniofacial features, mental retardation, and diffuse hypotonia. Distinct dysmorphic features included straight eyebrows, deep-set eyes, flat nasal bridge, midface hypoplasia, and pointed chin. All patients presented developmental delay, and different degrees of cognitive impairment, varying from profound or severe (87%) to moderate (13%).

None of the 91 patients had familial history of epileptic seizures. Five patients (5.5%) had transient perinatal distress, eight patients (8.8%) presented intrauterine growth retardation.

Electroclinical pattern

Seizures/epilepsy affected 53 out of the 91 patients (58.2%).

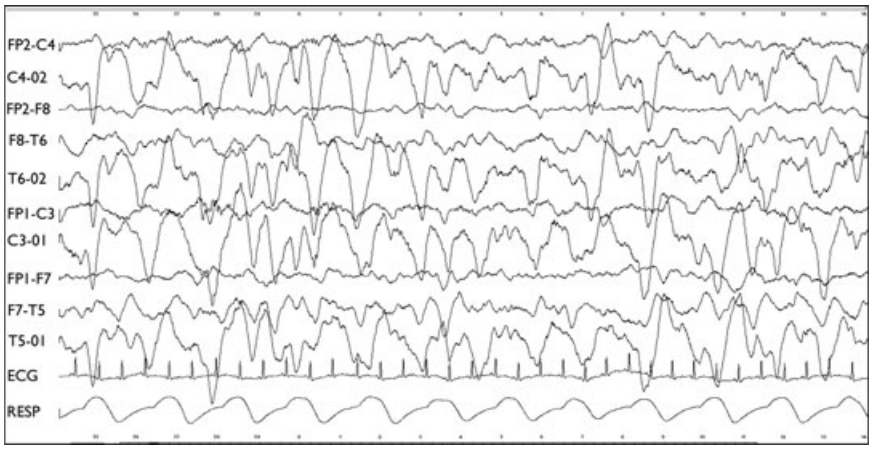

Figure 1.
Interictal sleep EEG of a patient of 2 months. Abnormal delta waves on both occipital regions. Four months later, this patient presented with hypsarrhythmia. Amplitude 10 μV/ mm; Speed 1 sec/cm.
Epilepsia © ILAE

First seizures

Seizures started during the first 6 months of life in 42 patients (79.2%), at the median age of 2.75 months. Neonatal seizures were reported in only three patients, with generalized tonic seizures in two cases, and complex partial seizures in one. In the remaining seven patients, seizures started within age 2 years 8 months. Only one patient had onset of atypical absences at the age of 15 years.

First seizures were described as generalized in 25 cases, being tonic in 8, tonic–clonic in 6, and clonic/myoclonic in 12. First seizures were simple partial in 6 cases or complex partial in 14. In seven cases, the presenting seizures were isolated infantile spasms (5/7) or combined with complex partial seizures (2/7).

Interictal EEG showed focal rolandic (6), temporoposterior temporooccipital (18), multifocal or generalized spikes, polyspikes, and spike/wave discharges (14 cases). Poverty of the usual physiological features, combined with abnormal delta–theta wave activity mainly over the posterior temporoparietooccipital areas, was seen in most patients (Fig. 1). Only three patients (two with epilepsy) had a normal EEG, and five showed an hypsarrhythmic EEG associated with infantile spasms at seizure onset.

Antiepileptic drugs (AEDs) were started in all but one patient (with only two seizures) after seizure diagnosis, with phenobarbital being the most common choice.

Thereafter, 29 patients (54.7%) were progressively controlled with AEDs. On the other hand, four cases (7.5%) continued with daily to weekly seizures with a combination of generalized tonic, myoclonic, and atonic seizures. The 20 remaining patients (37.7%) progressively developed infantile spasms.

Infantile spasms

Twenty patients developed an epileptic encephalopathy at a median age of 5 months (range 2–10 months). It combined infantile spasms with typical (14 cases) or modified hypsarrhythmia (6 cases) with a very slow EEG activity consisting of bilateral high-amplitude delta waves, intermixed with spikes and polyspikes on both frontal (2 cases), both central (3 cases), or both occipital (1 case) regions (Fig. 2).

High doses of oral steroids were tried in nine cases, with a prompt remission of seizures and resolution of EEG abnormalities in six patients, whereas three patients remained refractory to steroids. Among the six responders to steroids, five were seizure-free at the time of evaluation, and only one developed refractory epilepsy. Conversely, among the three nonresponders to steroids, two patients developed severe and refractory epilepsy.

When we consider the delay between the onset of infantile spasms and the introduction of steroids, the mean delay was 1.33 month for the good responders and 2 months for the nonresponders.

For the remaining 11 patients that developed infantile spasms, steroids were not tried. Instead, patients were treated with phenobarbital (five cases), vigabatrin (3), valproate (1), or benzodiazepine (2). All these patients developed early severe and refractory epilepsy. One patient, who had a good response to vigabatrin, became transiently seizure-free but experienced a late relapse with polymorphic and refractory seizure, 1 year later.

Long-term outcome

At the age of evaluation (median 7.8 years, range 1–25 years), 19 patients (35.9%) developed refractory epilepsy, 2 (3.8%) had a partial seizure control, and 32 (60.4%) were seizure-free.

Seizure semiology

For the 19 patients (35.9%) that developed refractory epilepsy, seizures were polymorphic. They included generalized tonic and tonic–clonic seizures in 13 cases, myoclonic seizures in 11, complex partial seizures in 3, atypical absences in 3, and atonic seizures in 2 patients. Strikingly, 15/19 (78.9%) previously presented epileptic encephalopathy with infantile spasms, refractory to steroids (2 cases), or nontreated with steroids (12 cases).

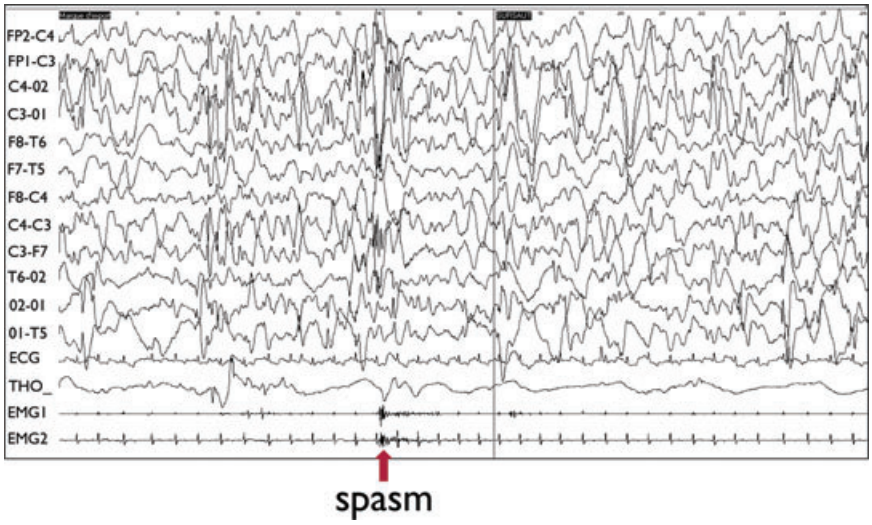

Figure 2.
Wakeness EEG of a patient of 8 months. Multifocal spikes predominating on both central regions. One recorded epileptic spasm associated with short tonic contraction on both surface EMG records and typical slow wave pattern on the EEG tracing. EMG1 right surface deltoid; EMG2 left surface deltoid; Amplitude 10 μV/ mm; Speed 1 sec/cm.
Epilepsia © ILAE

Two additional patients had a partial seizure control with an average of two seizures per month. Seizures were complex partial in both cases.

The remaining 32 patients (60.4%) had well-controlled epilepsy on the usual AEDs, and are seizure-free. Mean age of seizure arrest was 1.8 years (range 0.2–3 years), and seven patients were off medication since several years.

EEG findings

Interictal EEG remained abnormal in 46 of 53 patients (87.8%).

For the 19 patients that developed refractory seizures, interictal EEG remained abnormal in all cases and showed persistent multifocal or diffuse high-amplitude spikes mixed with irregular slow waves (Fig. 3).

For the two patients partially controlled with AEDs, EEG showed slow background activity with focal frontal spikes in one case and temporal spikes in the other case.

For the 32 seizure-free patients, EEG was either normal (7 cases), or showed slow background activity with poverty of the usual rhythmic activities (17 cases). In the other eight seizure-free patients, the EEG still showed paroxysmal activity with focal or generalized spike and wave discharges.

MRI findings

Brain magnetic resonance imaging (MRI) was performed in all patients with epilepsy at the median age of 1.5 years (range 2 months–5 years). Most common findings were cortical atrophy with enlargement of the lateral ventricles in 41 (77.4%) patients. Neither focal nor diffuse

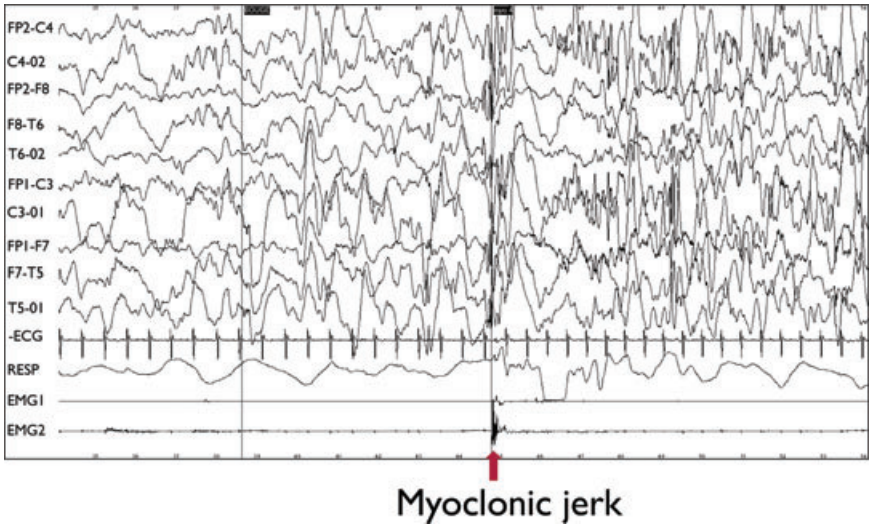

Figure 3.
Myoclonic jerk in a patient of 2 years; EMG1 right surface deltoid; EMG2 left surface deltoid; Amplitude 10 μV/ mm; Speed 1 sec/cm.
Epilepsia © ILAE

Table 1. Literature analysis of epilepsy findings in Del 1p36 syndrome

Series	Number of patients	History of seizures N (%)	Age of seizure onset (range)	Infantile spasms n (%)	Intractable epilepsy	Seizure types
Shapira et al. (1997)	13	9 (69.2%)		+	N/A	Simple partial/complex partial/myoclonic seizures
Knight-Jones et al. (2000)	4	4 (100%)	3 months–2 years	3	3	Complex partial/myoclonic/atonic seizures
Heilstedt et al. (2001)	24	14 (58.33%)		3	3	N/A
Heilstedt et al. (2003)	31	15 (48.4%)	N/A	+		Generalized tonic–clonic/myoclonic/complex partial seizures
Kurosawa et al. (2005)	11	8 (72.7%)	1 month –7 years		6	
Battaglia et al. (in press)	60	26 (44%)	4 days–2.5 years	15 (25%)	4	Generalized tonic–clonic/myoclonic/complex partial seizures

[a]Patients for whom clinical evaluation was available.
N/A, nonavailable.

cortical malformation was observed White matter abnormalities were observed in 20 cases (37.7%) that consisted in nonspecific posterior white matter abnormalities in 15 cases and delayed myelination in 5 cases. Thin corpus callosal was observed in five cases (9.4%). MRI was normal in five cases (9.4%).

Discussion

The present series is the largest sample of patients with Del 1p36 syndrome, so far, and allows a better delineation of the epilepsy phenotype in this common terminal deletion syndrome. Our results highlight that epilepsy is a significant and potentially treatable feature in patients with Del 1p36 syndrome.

The prevalence of epilepsy is 58.2% in keeping with previously reported data (Shapira et al., 1997; Knight-Jones et al., 2000; Heilstedt et al., 2001, 2003a; Kurosawa et al., 2005). In most patients (79.2%), epilepsy starts in infancy, during the first 6 months of life, but rarely in the neonatal period. As already reported, first seizures are usually generalized tonic, tonic–clonic, or clonic (Shapira et al., 1997; Knight-Jones et al., 2000; Heilstedt et al., 2001, 2003b; Kurosawa et al., 2005). Our data suggest that for these patients, EEG recordings are abnormal early on combining epileptiform abnormalities and poverty of physiological background rhythmic activities. Although seizure types are highly variable, infantile spasms are one of the most common (37.7%), occurring between 2 and 10 months of age, usually combined with other seizure types.

Epilepsy outcome is usually favorable but can be severe, since one-third of our patients had drug-resistant seizures. This prevalence of refractory epilepsy is difficult to compare to previous series (3/24 in Heldsteidt's series; 6/11 in Kurosawa's series; and 4/60 in Battaglia's series) due to the lack of information of these reports (Table 1) (Shapira et al., 1997; Knight-Jones et al., 2000; Heilstedt et al., 2001, 2003b; Kurosawa et al., 2005; Battaglia et al., 2005). However, we cannot exclude the fact that such a degree of therapy resistance could be related with the fact that most patients of our sample were enrolled through neuropediatric clinics.

Our data suggest that the onset of refractory epilepsy in Del 1p36 syndrome might be associated with (1) the onset of infantile spasms and (2) their quality of response to high-dose steroids. Indeed, among the patients with refractory epilepsy, 78.9% (15/19) patients previously presented infantile spasms. Among these patients, 80% (12/15) were not treated with steroids, but instead with various AED. On the contrary, when infantile spasms were controlled by steroids, refractory epilepsy tends to less develop (only one of six good responders) and seizure freedom is more frequent. As a consequence, our data might suggest that when infantile spasm occurs in Del 1p36, high-dose steroid treatment is key to successful treatment of the epilepsy.

Several studies have pointed out the importance of early treatment in infantile spasms (Jeavons et al., 1973; Jambaque et al., 2000). Similarly, we hypothesized that the poor response of infantile spasms to steroids observed in three of nine of our patients might be related to the time lag between infantile spasms onset and its treatment. However, our data do not confirm this hypothesis. Further studies on larger samples of Del 1p36 children with infantile spasms should help defining whether early treatment influences the global neurodevelopmental outcome as in Down syndrome (Eisermann et al., 2003).

Our data also underline that epilepsy outcome is highly variable between patients with Del 1p36 syndrome. This clinical variability observed in the epilepsy outcome of patients have already been underlined for the other features of Del 1p36 syndrome, that is, hearing loss, hypothyroidism, growth retardation, and heart defect. These differences in the clinical phenotype in Del 1p36 syndrome may be related with the variation of the deletion size and, to a lesser

extent, with the effects of imprinted genes (Shapira et al., 1997; Heilstedt et al., 2001).

Pathophysiological mechanisms of epilepsy in Del 1p36 syndrome remain unknown. Many genes are deleted in Del 1p36 patients because the area of deletion can be variable (<32 centimorgan) (Wu et al., 1999). Since the terminal region of chromosome 1p is gene-rich, multiple genes, when hemizygous, may contribute to the various phenotypic features in this syndrome (Shapira et al., 1997; Knight-Jones et al., 2000; Windpassinger et al., 2002; Heilstedt et al., 2003b). Among these, two major genes included the 1p36 region might account for epilepsy, KCNAB2, a voltage-gated potassium channel β-subunit gene (Heilstedt et al., 2001), GABRD, the human γ-aminobutyric acid A receptor delta-subunit gene (Windpassinger et al., 2002).

Heildstedt et al. reported that haploinsufficiency for KCNAB2 may contribute for epilepsy in Del1p36 syndrome (Heilstedt et al., 2001). In that situation, the functional loss of one KCNAB2 allele decreases the threshold for seizures, by reducing potassium channel-mediated membrane repolarization and increasing neuronal excitability (Heilstedt et al., 2001). However, their results combined with recent reports give conflicting results on the implication of KCNAB2 haploinsufficiency, since a significant proportion of patients with del 1p36 had intractable epilepsy without loss of KCNAB2 (2/8 and 4/11 patients with epilepsy in Kurosawa's series and in Heildstedt's series, respectively). Conversely, other patients never developed epilepsy but were deleted for this gene (1/5 and 1/13 patients without epilepsy in Kurosawa's series and Heildstedt's series, respectively) (Heilstedt et al., 2001; Kurosawa et al., 2005).

Another gene, the human γ-aminobutyric acid A receptor delta-subunit gene (GABRD) has also been suggested to contribute to epilepsy in Del 1p36 syndrome. These findings were obtained by mapping the gene expression within the critical region deleted in most patients with Del 1p36 syndrome, but no correlation with the genotype were presented (Windpassinger et al., 2002). These data stimulate further phenotype–genotype correlation studies in order to search for causative genes for epilepsy in Del 1p36 syndrome.

Among the few genetic causes of infantile spasms, Del 1p36 is to be kept in mind. The other known genetic causes of infantile spasms without visible lesions on MRI are trisomy 21 (Stafstrom & Konkol, 1994; Silva et al., 1996) and mutations of ARX (Stromme et al., 2002) or CDKL5 genes (Weaving et al., 2004). However, no neurophysiological link has been found between such abnormalities and infantile spasms. As infantile spasms are age-dependant epileptic encephalopathies, we would hypothesize that these and/or other, as yet unknown, genes can, when mutated, alter the neuronal excitability at a specific period of development, giving rise to this catastrophic epileptic encephalopathy.

Conclusions

Our observations suggest that Del 1p36 syndrome represent a significant cause of infantile spasms. Clinicians should be aware of this epilepsy phenotype that can be treated, but when left untreated can lead to further difficulties. On the contrary, Del 1p36 should be searched for in patients presenting with infantile spasms associated with a hypsarrhythmic EEG, particularly if they are combined with dysmorphic features, severe hypotonia, and developmental delay.

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Conflict of interest: None of the authors has any conflict of interest to disclose.

We confirm that we have read the Journals position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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