

# Angelman syndrome and pseudo-hypsarrhythmia: a diagnostic pitfall

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**ABSTRACT** – Angelman syndrome is a rare genetic disorder scarcely diagnosed before the age of two years. We report the case of an eight-month-old female presenting with severe hypotonia, myoclonus, suspected spasms and an electroencephalogram with hypsarrhythmic-like features. She was initially treated with vigabatrin which resulted in worsening of myoclonic jerks. Fluorometric *in situ* hybridization revealed a chromosomal deletion at region 15q11-13. We discuss the case and differential diagnosis with other conditions including West syndrome. [Published with video sequences]

**Key words:** Angelman syndrome, myoclonus, hypsarrhythmia, West syndrome, AEDs aggravation

Angelman syndrome (AS) is a rare genetic disorder first described by Harry Angelman in 1965 (Angelman, 1965). The typical phenotypic features comprise severe mental retardation, inappropriate laughter, a happy disposition, ataxic gait, jerky movements, and absent or minimal speech (Boyd *et al.*, 1988; Buoni *et al.*, 1999; Van Lierde *et al.*, 1990). The disorder was previously described as “happy puppet syndrome”, however, this clinical entity has since been renamed “Angelman syndrome” and much more is now known regarding genetic determinants. AS is one of the best human models of genomic imprinting and involves expression of the maternally inherited allele of the

*UBE3A* gene, located at chromosomal region 15q11-13 (Buoni *et al.*, 1999). A microdeletion of this region is present in 70% of cases, and is responsible for a more severe phenotype (Dan, 2009; Guerrini *et al.*, 2003). Other genetic abnormalities are uniparental paternal disomy, mutation of the imprinting centre or intragenic mutation of the *UBE3A* gene (Guerrini *et al.*, 2003; Buoni *et al.*, 1999). More than 80% of patients with AS experience seizures, and epilepsy is often severe and resistant to antiepileptic drugs (Laan *et al.*, 1997; Guerrini *et al.*, 2003). An abnormal EEG pattern, characterised by large-amplitude slow spike-waves, is often present even in the absence of



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seizures, and has been proposed as a tool for early diagnosis (Williams *et al.*, 2001; Boyd *et al.*, 1988; Valente *et al.*, 2003; Laan *et al.*, 1997). However, because clinical traits generally become evident by the age of three to four years, diagnosis is rarely made before this stage (Valente *et al.*, 2003; Guerrini *et al.*, 2003).

Here, we report the case of an eight-month-old female who presented with severe hypotonia, suspected infantile spasms, myoclonic jerks and an EEG with hypsarrhythmic-like features. A cytogenetic study revealed a deletion of the chromosome region 15q11-13. We further discuss possible misdiagnosis of patients with AS who present with pseudo-hypsarrhythmia.

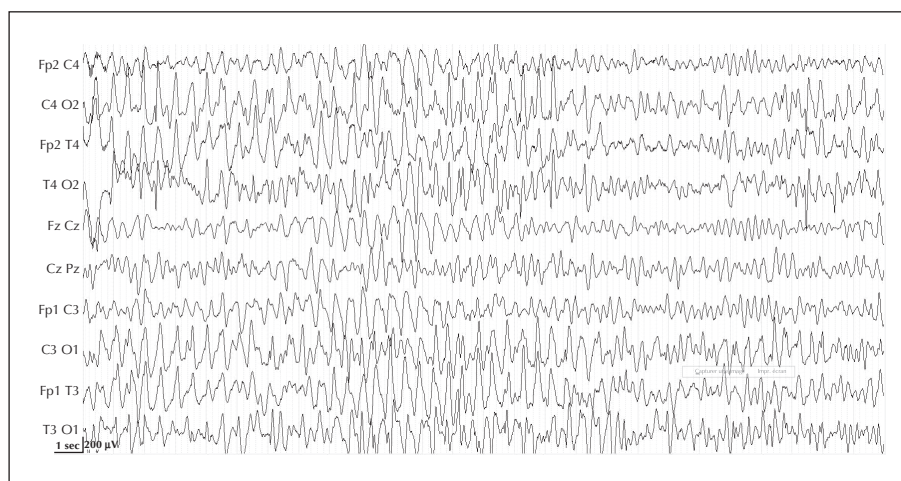
## Case study

A seven-month-old female infant was hospitalised in our paediatric department for suspicion of infantile spasms. She was the first child of a non-related couple without familial history of epilepsy or neurological impairment. Pregnancy was followed normally to term, with uncomplicated delivery and birth. At three months, she began to experience feeding difficulties, distal tremor of the hands and made unusual cries. Spasms were suspected by her physician and she was referred to our department. On admission, she had moderate growth retardation with normal cephalic perimeter. She was severely hypotonic and presented with jerky movements of her extremities impairing voluntary prehension. She had light skin and bright hair. Her facial traits were unremarkable. A first EEG recorded on admission revealed an abnormally slow and poorly organised awake pattern with few spikes and slow-wave spikes over temporal regions. Sleep

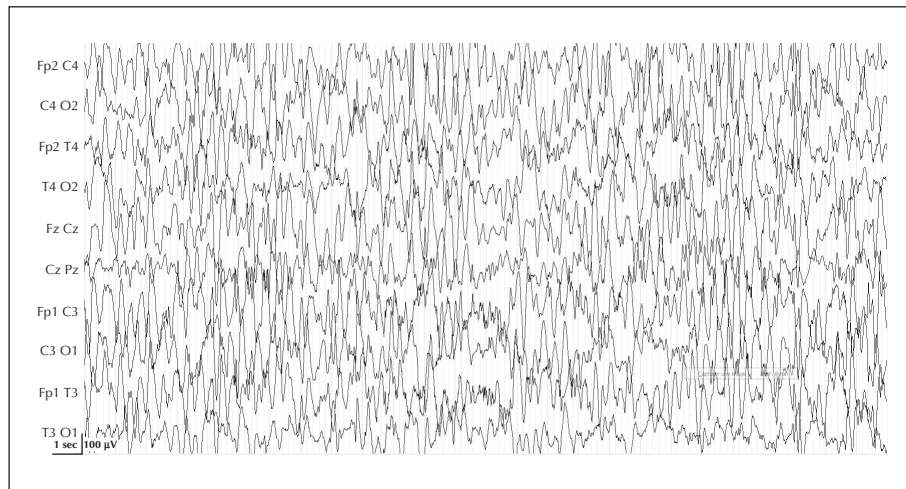
organisation was abnormal with poor physiological features. No electrical spasms were recorded (*figure 1*). During the following days, clinical spasms were observed by the paediatric team, and another EEG was consistent with hypsarrhythmia (*figure 2*). EEG tracing did not show any detectable seizures. An antiepileptic treatment with vigabatrin at 100 mg/kg/day was then started, resulting in worsening of myoclonic jerks and feeding problems. Brain MRI showed no particular abnormalities. Lumbar puncture and metabolic screening tests were normal. Fundus showed retinal hypopigmentation. Treatment with adrenocorticotrophin, thiamine, folinic acid and biotin was initiated and the patient's general status ameliorated, but myoclonus persisted and inappropriate laughter was noticed. Myoclonus totally disappeared during sleep, and was not correlated with spikes on EEG (see *video sequence*). Back averaging, however, showed a correlation with slow spike predominance over central regions and vertex. The evolution was consistent with non-progressive myoclonic epilepsy, and screening for AS and Rett syndrome (*MECP2* mutations) was conducted. At the same time, the EEG became less hypsarrhythmic, showing a classic delta pattern (*figure 3*). Fluorometric *in situ* hybridization (FISH) revealed a deletion at chromosome region 15q11-13, consistent with AS. Antiepileptic treatment was then changed, and she received a combination of valproate and clonazepam.

## Discussion

In infants and toddlers with Angelman syndrome the association between infantile spasms (IS) and an EEG with hypsarrhythmic-like features is rare



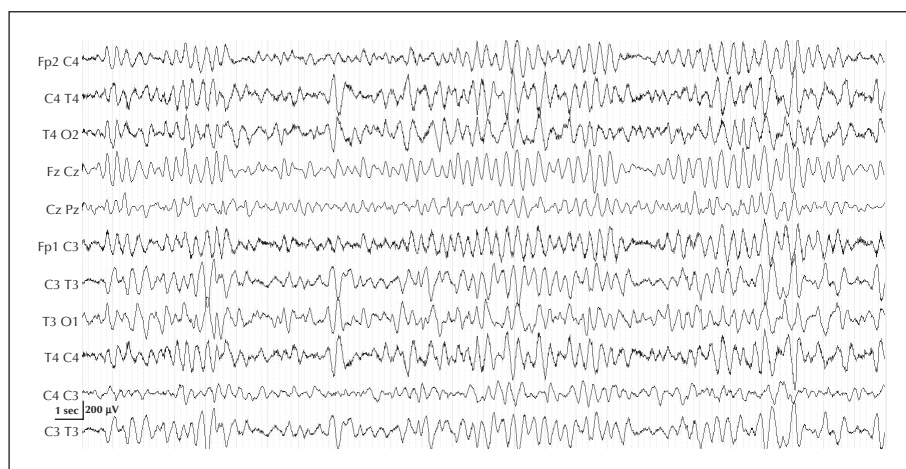
**Figure 1.** EEG recording showing abnormal pattern during wakefulness with runs of 2-3-Hz high amplitude and synchronous slow waves predominant over posterior regions associated with few spikes and slow-wave spikes over temporal regions. Low filter: 0.53 Hz; high filter: 60 Hz.



**Figure 2.** EEG recording during wakefulness showing high-amplitude generalised delta waves with a certain degree of interhemispheric synchronisation and associated multifocal paroxysmal discharges. Low filter: 0.53 Hz; high filter: 60 Hz.

but has already been described (Boyd *et al.*, 1988; Buoni *et al.*, 1999; Guerrini *et al.*, 2003; Uemura *et al.*, 2005). As characteristic phenotypic features (such as happy demeanor, microcephalia or typical facial traits) may appear later in life, there is, in our opinion, a diagnostic pitfall that must be taken into consideration, given the fact that epilepsy of West syndrome usually responds to drugs that may worsen symptoms in patients with AS (Guerrini *et al.*, 2003). In fact, worsening of myoclonus and absence seizures has already been reported with vigabatrin, which was the case with our patient (Guerrini *et al.*, 2003). Several studies have shown the presence of EEG patterns to be compatible with hypsarrhythmia in patients with AS (Buoni *et al.*, 1999; Uemura *et al.*, 2005; Valente *et al.*, 2003). Valente *et al.* in 2003 reviewed serial EEGs of 26 patients with clinical diagnosis consistent with AS, of which

22 had genetic confirmation. Three patients showed a hypsarrhythmic-like pattern, exclusively before the age of two years. For the authors, EEG tracing resembled hypsarrhythmia but differed on the basis of predominance of slow waves over epileptiform discharges and the lack of correlation with sleep and awake status. The fragmentation described during sleep by Hrachovy *et al.* in 1981 was also not observed. On the other hand, the same authors in 1984 studied variants of hypsarrhythmia, in particular with increased interhemispheric synchronisation that may resemble AS high-voltage patterns (Hrachovy *et al.*, 1984). Thus, on the sole basis of EEG recordings, confusion is possible. Uemura *et al.* in 2005 conducted a long-term study of EEG patterns of 23 patients with the microdeletion type of AS. They found two patients aged less than two years presenting with hypsarrhythmia. Interestingly,



**Figure 3.** EEG recording during wakefulness showing runs of synchronous high-amplitude delta waves predominant over anterior regions. Low filter: 0.53 Hz; high filter: 60 Hz.

they both had initial myoclonic seizures starting in the first two years of life but were diagnosed at ages 14 and 15 years, respectively. This underlines the possible gap between initial misdiagnosis of West syndrome and correct diagnosis of AS. However, as in our case, myoclonus is very uncommon in West syndrome and this is why confirmation of cortical origin by means of back averaging is of crucial importance (Dulac et al., 1998; Guerrini et al., 2003). Furthermore, this quasi-continuous tremor-like movement disappeared in our video-EEG recording during sleep, which is consistent with myoclonus observed in AS (Dulac et al., 1998; Guerrini et al., 2003). Finally, suspicion of infantile spasms probably influenced the interpretation of EEG, even if absence of recorded spasms and association with myoclonus was particularly unusual.

Several studies have attempted to define the classic EEG aspects observed in AS (Boyd et al., 1988; Buoni et al., 1999; Guerrini et al., 2003; Laan et al., 1997). EEG seems to be a very sensitive method for the diagnosis of AS, in up to 96% cases (Valente et al., 2003), being present in nearly half of patients before seizures have begun (Laan et al., 1997). Our EEG recordings finally showed a classic delta pattern (Valente et al., 2003). GABA-related excessive neuronal synchrony has been proposed to explain such EEG features (Dan, 2009). This could represent a model of thalamo-cortical dysfunction linked with alteration of the ubiquitin pathway and regulation of GABA<sub>A</sub> B3 subunit receptor (Dan, 2009). The occurrence of an age-specific (three months to two years) hypsarrhythmic pattern could be explained by exaggerated cortical excitability characteristic of this brain maturation period.

Early diagnosis of AS by means of EEG has already been reported in the literature (Van Lierde et al., 1990; Ostergaard and Juhl, 1997). Systematic EEG recordings in young children with delayed development have been proposed to rule out AS (Valente et al., 2003). However, it is of importance to remember that AS classic EEG patterns may also be observed in other conditions, such as Rett syndrome or 4p deletion syndrome (Valente et al., 2003; Williams et al., 2001; Watson et al., 2001). Moreover, non-progressive myoclonic epilepsy is not specific to AS and should lead the clinician to rule out other possible causes, such as brain malformations, metabolic disorders (thiamine deficiency, mitochondrial disorders, etc) or other genetically determined epilepsies (Rett syndrome, *CDKL5* or *ARX* mutations, etc). In the present case, it is probable that early onset of epilepsy and suggestive clinical traits, such as hypotonia, myoclonus, inappropriate laughter and pseudo-albinism, reflect a severe phenotype, mainly observed in the deletion type of AS.

This observation is of interest because diagnosis of AS before one year of age is rare and has been scarcely

reported throughout the literature. This may be linked to particularly severe phenotypes. Furthermore, during infancy, association with pseudo-hypsarrhythmia, hypotonia and myoclonic jerks which disappear during sleep should be highly suggestive of the deletion type of AS. A pseudo-hypsarrhythmic EEG pattern may therefore represent a diagnostic pitfall leading to delay of appropriate treatment and correct genetic investigations. □

#### Disclosure.

None of the authors has any conflict of interest or financial support to disclose.

### Legend for video sequence

Video sequence showing bursts of generalised myoclonus upon awakening.

**Key words for video research**  
on [www.epilepticdisorders.com](http://www.epilepticdisorders.com)

*Etiology:* angelman syndrome

*Phenomenology:* myoclonic seizure; spasm (epileptic)

*Localization:* —

*Syndrome:* myoclonic encephalopathy in nonprogressive disorders

### References

- Angelman H. "Puppet" children: a report of three cases. *Developmental medicine and child neurology*. London: Mackeith Press, 1965.
- Boyd SG, Harden A, Patton MA. The EEG in early diagnosis of the Angelman (happy puppet) syndrome. *Eur J Pediatr* 1988; 147: 508-13.
- Buoni S, Grosso S, Pucci L, et al. Diagnosis of Angelman syndrome: clinical and EEG criteria. *Brain Dev* 1999; 21: 296-302.
- Dan B. Angelman syndrome: current understanding and research prospects. *Epilepsia* 2009; 50: 2331-9.
- Dulac O, Plouin P, Shewmon A. Myoclonus and epilepsy in childhood: 1996 Royaumont meeting. *Epilepsy Res* 1998; 30: 91-106.
- Guerrini R, Carrozzo R, Rinaldi R, et al. Angelman syndrome: etiology, clinical features, diagnosis, and management of symptoms. *Paediatr Drugs* 2003; 5: 647-61.
- Hrachovy RA, Frost JD, Kellaway P. Sleep characteristics in infantile spasms. *Neurology* 1981; 31: 688-93.
- Hrachovy RA, Frost JD, Kellaway P. Hypsarrhythmia: variations on the theme. *Epilepsia* 1984; 25: 317-325.
- Laan LA, Renier WO, Arts WF, et al. Evolution of epilepsy and EEG findings in Angelman syndrome. *Epilepsia* 1997; 38: 195-9.

Ostergaard JR, Juhl AH. EEG and early diagnosis of Angelman syndrome. *Ugeskr Laeg* 1997;159:1273-6.

Uemura N, Matsumoto A, Nakamura M, *et al.* Evolution of seizures and electroencephalographical findings in 23 cases of deletion type Angelman syndrome. *Brain Dev* 2005;27:383-8.

Valente KD, Andrade JQ, Grossmann RM, *et al.* Angelman syndrome: difficulties in EEG pattern recognition and possible misinterpretations. *Epilepsia* 2003;44:1051-63.

Van Lierde A, Atza MG, Giardino D, Viani F. Angelman's syndrome in the first year of life. *Dev Med Child Neurol* 1990;32:1011-6.

Watson P, Black G, Ramsden S, *et al.* Angelman syndrome phenotype associated with mutations in MECP2, a gene encoding a methyl CpG binding protein. *J Med Genet* 2001;38:224-8.

Williams CA, Lossie A, Driscoll D, R.C. Phillips Unit. Angelman syndrome: mimicking conditions and phenotypes. *Am J Med Genet* 2001;101:59-64.