

# Catatonic psychosis related to forced normalization in a girl with Dravet's syndrome

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**ABSTRACT** – It has been reported that the clinical presentation of forced normalization can vary from paranoid hallucinatory states to anxiety and conversion phenomena, and that it may occur in both generalised and focal epilepsies. On the basis of the evaluation of a video recording, we found that forced normalization was concomitant with catatonic psychosis in a patient with epilepsy, intellectual disability and pervasive developmental disorder. Catatonic psychosis accompanying forced normalization has not been previously reported. As the psychotic symptoms and quality of life worsen seizure control improves, we believe it may be better for the patient to tolerate some seizures, thus preserving their capacity to interact socially. [*Published with video sequences*]

**Key words:** forced normalization, catatonic psychosis, epilepsy, anxiety

The relationship between recurring epileptic seizures and episodes of psychiatric disorders is a characteristic alternating pattern of events that has long been recognised. In 1953, Landolt introduced EEG recordings as a means of better elucidating this peculiar antagonism, and coined the term “paradoxical” or “forced EEG normalization” (Landolt 1953, 1958, 1963), stating that “forced normalization is a phenomenon characterised by the fact that, with the occurrence of psychotic states, the EEG ameliorates, or becomes entirely normal, as compared with previous and subsequent EEG findings”. Further studies have confirmed the existence of forced normalization, with the patterns being referred to by their authors as “transformed epilepsy” or “epileptic equivalent” (Schmitz 1998), or “alternative psychosis” (Tellenbach 1965).

The clinical presentation of forced normalization has been described as varying from paranoid hallucinatory states to anxiety and conversion phenomena (Wolf 1984, Wolf-Trimble 1985), and has been found to occur in both generalised and focal epilepsies (Wolf 1991). Most anti-epileptic drugs and, more recently, vagal nerve stimulation are thought to be involved (Schmitz 2006, Gatzonis *et al.* 2000). Patients with multiple daily seizures and previous epilepsy-related, psychiatric disorders seem to be more vulnerable (Wolf 1991), whereas forced normalization has only been rarely reported in children and adolescents (Amir and Gross-Tsur 1994). Various mechanisms have been proposed as underlying the antagonistic relationship between epileptic activity and psychosis, including an imbalance of inhibition and over-



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activation, kindling processes, the propagation of epileptic discharges along unusual pathways, and neurotransmitter alterations (Landolt 1958, Wolf 1991, Krishnamoorthy and Trimble 1999).

We have recently treated a patient with Dravet's syndrome, mental retardation and behavioural problems including pervasive developmental disorder (PDD), who experienced one episode of forced normalization of the EEG pattern and a one-month, seizure-free period. We discuss here the treatment options and the management of an event that could be misdiagnosed in young patients with language disability and PDD.

## Case report

A 14-year-old girl, affected by Dravet's syndrome, severe mental retardation and PDD, was first admitted to our hospital in Bologna in April 2004 because of a sudden behavioural change consisting of the absence of understandable language, slowed motor activity, a catatonic posture maintained for some minutes, indifference to people and the environment, and a very poor food intake. The first child of healthy and non-consanguineous parents, she was born at term after a normal pregnancy with a birth weight of 3 940 g. Gross, early neonatal motor development was almost normal but, from the age of three, she experienced psychomotor developmental regression mainly involving the linguistic area. Her epilepsy began with myoclonic seizures when she was seven months old. The seizures, which were sporadic at first but became increasingly frequent (several times per month), were characterised by a loss of consciousness,

unilateral or bilateral clonic movements (predominantly on the right side), and sometimes lasted for more than 30 minutes (status epilepticus). They mainly occurred during awakening or when the patient was falling asleep.

At the age of one year, she was admitted to another hospital. Because of the seizures and EEG abnormalities, treatments with phenobarbital, carbamazepine and sodium valproate were tried but were ineffective. The results of metabolic tests, brain MRI and electrophysiological examinations were normal, and she was discharged with the diagnosis of severe myoclonic epilepsy (Dravet syndrome).

Because of the persistence of the seizures, various anti-epileptic drugs were tried during subsequent years (clobazam, ethosuximide, nitrazepam, vigabatrin, clonazepam, and lamotrigine), without any meaningful result. The epileptic seizures usually occurred during the night, were grouped in clusters, and their frequency varied from a few times per month to several times per day.

When she was 11 years old, topiramate was started and partially controlled the seizures. For this reason, a ketogenic diet was tried. However, this led to no improvement and caused side effects such as recurrent respiratory infections.

As mentioned above, the child's psychomotor development (mainly in the linguistic area) had been delayed since the age of three years, and subsequently she progressively developed PDD, showing poor social interaction but without any signs of aggressiveness or psychosis.

A number of interictal EEG recordings showed monomorphic theta activity and rare right fronto-central spikes (figure 1).

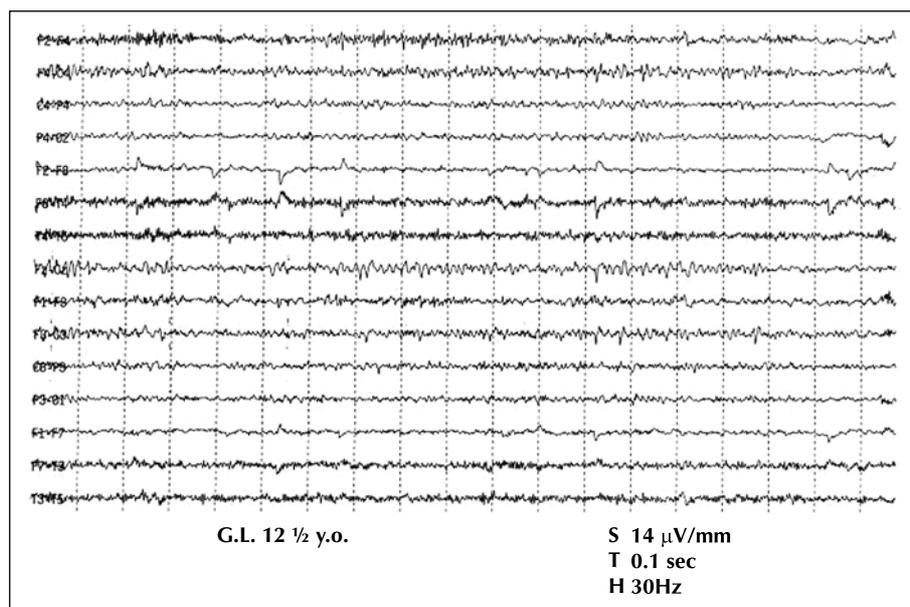


Figure 1. Bilateral, notched theta activity over the central regions.

Molecular analysis of the SCN1A gene revealed a heterozygous nucleotide substitution of C to T at base position 1129 in the exon 8 coding sequence, which caused the insertion of a stop codon at position 377 (R377X). The parents did not carry the same mutation.

When the patient was 14 years old (just one month before our observation), the seizures that had occurred several times per month rapidly became less frequent and then disappeared, despite there having been no change in her treatment with phenobarbital (2.3 mg/kg/day), topiramate (7.1 mg/kg/day) and clobazam (0.05 mg/kg/day). When she was completely seizure-free, an EEG revealed a resolution of paroxysmal discharges; background activity, including spindles and humps, was poorly organised and slow activity was evident on the right temporal region (*figure 2*). At the same time, her behaviour progressively changed and she experienced a psychotic regression, with very slow motor activity, the absence of any social or environmental interactions, apathy, and passivity. Interestingly, she tended to assume and maintain plastic postures for a long time mimicking catatonia. Language, which had usually been present albeit delayed, was totally absent during this psychotic regression (*see video sequence*).

At our first evaluation, we related this phenomenon to her severe cognitive disability. However, the EEG normalization and abrupt disappearance of seizures suggested the phenomenon of forced normalization and so we decided to reduce the daily dose of phenobarbital to 1.7 mg/kg. After that, the myoclonic seizures reappeared and the EEG

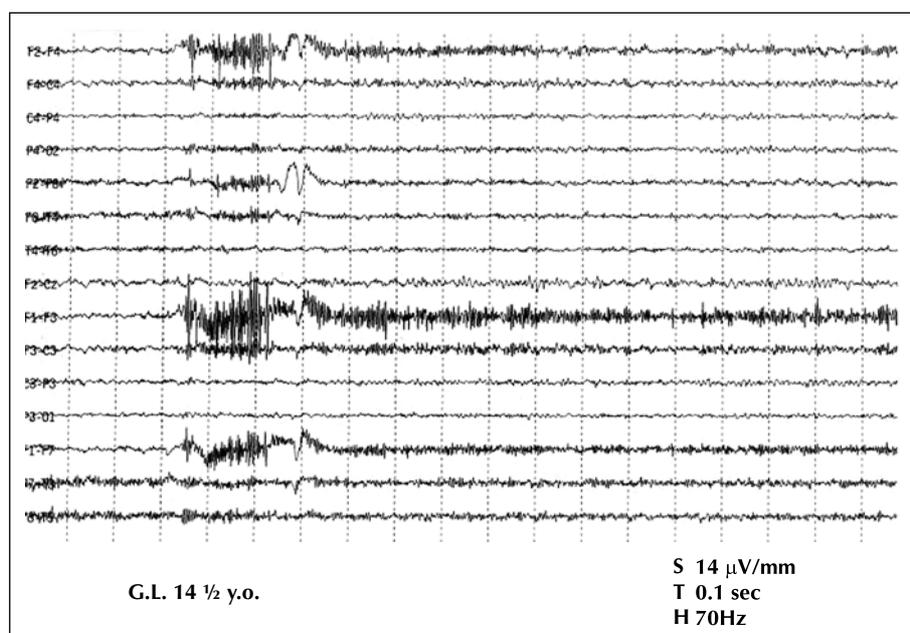
findings reverted to their previous state (*figure 3*); however, her behaviour greatly improved and the catatonia disappeared (*see video sequence*).

## Discussion

Forced normalization has been known about for a long time, but the current literature is scarce and the majority of published papers are case reports. The main reason for this is that the lack of clear diagnostic criteria has halted research in the field. One of the really challenging problems of forced normalization is whether it should be considered as encompassing cases with a relatively normalised EEG pattern or restricted to those that are completely normalised. Another important issue is the relationship between EEG normalization, the absence of seizures, and the duration of the associated psychosis.

Forced normalization does not seem to be limited to drug-induced seizure control. Krishnamoorthy and Trimble (1999) suggested a broader approach that would include cases with fewer seizures during the psychotic status and an only relatively normalised EEG, and proposed both primary (essential) and supportive diagnostic criteria.

The primary criteria include: 1) an established diagnosis of epilepsy; 2) the presence of behavioural disturbances with an acute/subacute onset (including psychosis, mood changes and anxiety disorders); 3) a reduction in the total number of spikes per hour in more than 50% of the awake



**Figure 2.** EEG during forced normalization. Note not only the absence of bilateral, central theta activity, but also the absence of alpha rhythm due to the acute psychosis and difficulties in relaxing.



**Figure 3.** EEG recording after forced normalization. Note the reappearance of alpha rhythm and right abnormalities over the fronto-central regions.

EEG recordings; and 4) a report of the complete absence of seizures for at least one week.

The supportive criteria include: 1) a recent change (within 30 days) of the pharmacotherapeutic regimen; and 2) a report of similar episodes of the absence of seizures and the presence of behavioural disturbances in the past.

Furthermore, some factors apparently facilitate the onset of forced normalization, including chronic epilepsy (better if focal and originating from the limbic lobe), previous epilepsy-related behavioural problems, sleep disturbances, and psychosocial factors (Wolf 1991).

Our patient seems to fulfil the primary criteria for forced normalization, which make patients more susceptible to its occurrence regardless of other provoking factors such as a recent change in the drug regimen; however the pathogenesis of forced normalization remains unclear (Wolf 1991).

We thought it is interesting to describe this case because it involves an episode of forced normalization that was characterised by catatonic symptoms and overlapped a previous behavioural and psychopathological picture characterised by an autistic approach to reality and difficulties mainly in social interaction, and the fact that such a picture may be subject to a mistaken or delayed diagnosis. Furthermore, a catatonic picture has not previously been described in association with forced normalization. Intellectual disability could itself contribute towards a delayed diagnosis because of the difficulty in approaching the patient, as suggested by other case reports (Yamamoto *et al.* 2001, Amir and Gross-Tsur 1994). However, the

presence of our patient's intellectual disability makes her case even more informative because, in line with the observations of other authors (Pfanner *et al.* 2000), it shows that intellectually disabled brains can produce psychiatric disorders exactly like those produced by normal brains.

Finally, the resolution of the forced normalization required a reduction in the dose of the ongoing anti-epileptic therapy and this significantly improved the patient's quality of life despite the worsened seizure control. This reminds us that the quality of life of a patient with epilepsy comprises several factors and should not be considered simply in terms of seizure control.

In conclusion, unlike in pre- and post-ictal dysphoric patients, who can benefit from appropriate psychotropic therapy such as the use of atypical antipsychotics, in forced normalization patients, it may be preferable to tolerate more seizures (especially when they occur mainly at night) in order to preserve their capacity for social interaction. □

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## Legends for video sequences

### Sequence 1

During forced normalization: our patient experienced a behavioural change consisting in apathy, absence of understandable language, slowed motor activity, a catatonic posture maintained for some minutes and indifference to people and environment.

### Sequence 2

After forced normalization: after reducing daily dose of phenobarbital, patient's behaviour improved and ability to talk and smiling reappeared.

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