Original article

Epileptic negative drop attacks in atypical benign partial epilepsy: a neurophysiological study

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ABSTRACT – *Purpose*. We conducted a computer-assisted polygraphic analysis of drop attacks in a child with atypical benign partial epilepsy (ABPE) to investigate neurophysiological characteristics. *Subject and methods*. The patient was a six-year two-month-old girl, who had started to have focal motor seizures, later combined with daily epileptic negative myoclonus (ENM) and drop attacks, causing multiple injuries. We studied episodes of ENM and drop attacks using video-polygraphic and computer-assisted back-averaging analysis. *Results*. A total of 12 ENM episodes, seven involving the left arm (ENMlt) and five involving both arms (ENMbil), and five drop attacks were captured for analysis. All episodes were time-locked to spike-and-wave complexes (SWC) arising from both centro-temporo-parietal (CTP) areas. The latency between the onset of SWC and ENMlt, ENMbil, and drop attacks reached 68 ms, 42 ms, and 8 ms, respectively. The height of the spike as well as the slow-wave component of SWC for drop attacks were significantly larger than that for both ENMlt and ENMbil ($p < 0.05$). *Conclusion*. Drop attacks were considered to be epileptic negative myoclonus involving not only upper proximal but also axial muscles, causing the body to fall. Thus, drop attacks in ABPE are considered to be epileptic negative drop attacks arising from bilateral CTP foci and differ from drop attacks of a generalized origin seen in Lennox-Gastaut syndrome and myoclonic-astatic epilepsy.

Key words: atypical benign partial epilepsy, epileptic negative myoclonus, drop attacks

It is widely accepted that Lennox-Gastaut syndrome (LGS) and myoclonic-astatic epilepsy (MAE) are two epileptic syndromes that classically involve recurrent drop attacks (Beaumanoir and Blume 2005, Oguni *et al*. 2001). However, less attention has been paid to patients with atypical benign partial epilepsy (ABPE) in childhood, whose main seizure type has been described as recur-rent drop attacks (Aicardi and Chevrie 1982, Deonna *et al*. 1986, Oguni *et al*. 1992). ABPE is a special type of epileptic syndrome first described by Aicardi and Chevrie in 1982, characterized by: onset at between 2 and 6 years, multiple seizure types including focal motor seizures, atypical absence seizures or atonic seizures, the absence of developmental and neurological deficits prior to onset, focal

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epileptic EEG abnormality during wakefulness and generalized continuous slow spike-waves during sleep, and favorable seizure and intellectual prognoses (Aicardi and Chevrie 1982). These authors stressed the close similarity of clinical and EEG manifestations with those of LGS and MAE, and the differential diagnosis relative to these two syndromes. In this report, we investigated a patient with ABPE who had recurrent ENM and drop attacks that caused serious injury. We herein report the results of video-polygraphic and computer-assisted polygraphic analysis of drop attacks associated with ABPE, clarifying the neurophysiological nature of the patient and differences relative to LGS and MAE.

Subject

The girl was seven years and two months old during the final follow-up period. Regarding her family history, her paternal aunt had a history of childhood epilepsy. The girl was born uneventfully at 40 weeks gestation, weighing 3,360 grams. She was diagnosed with a small ventricular septal defect at two days old. She achieved normal developmental milestones. She experienced a febrile status epilepticus (SE) lasting one hour without sequel at one year and 11 months of age, and was diagnosed with complex febrile seizures. She experienced a second episode of febrile SE lasting 40 minutes at three years of age when she was given carbamazepine (CBZ) at a local hospital. She developed eye-blinking seizures before sleeping, which soon changed to focal twitching of her cheeks at four years and five months of age. In addition, she also demonstrated recurrent head-nodding attacks during wakefulness. These attacks increased in frequency at five years of age, despite an increased dosage of CBZ and a combination of valproate (VPA) and zonisamide (ZNS). Four months later, she started to have recurrent drop attacks, characterized by sudden backward or forward falls when sitting, and sudden collapsing onto the buttocks when standing. She recovered quickly from each episode but suffered recurrent head injuries due to the frequent drop attacks. She was referred to our clinic at six years and two months of age. She appeared healthy, with no physical or neurological abnormalities other than a systolic heart murmur of the left chest. During the clinical examination and video-polygraphic study, the girl presented frequent epileptic negative myoclonus, involving the left arm (ENMlt) or both arms (ENMbil), and drop attacks.

Methods

The attacks were investigated by means of simultaneous video-polygraphic recording. The surface electromyogram (EMG) was placed on both deltoid muscles. The EEG was recorded with 7 silver-silver chloride electrodes positioned according to the 10-20 method with the ears linked together. The polygraphic data were sampled at 512 Hz, and analyzed with Nihon-Koden based back-averaging software. The trigger points on the EMG (the onset of EMG silent period associated with drop attacks and ENM) were identified manually by reviewing all of the attacks. We measured the latency between the negative spike peak of spike-wave complexes (SWC) at electrode C4 and EMG trigger points. In addition, we measured the height of the spike as well as the slow-wave component of SWC (from the negative to positive peak) at electrode C4 and compared the data with those of ENM and drop attacks (Oguni *et al.* 1992, Parmeggiani *et al.* 2004). Student's t-tests were used for comparisons between the two groups. Bonferroni correction was made for multiple comparisons. $p < 0.05$ was considered to indicate a significant difference.

Results

The interictal waking EEG demonstrated posterior dominant 8 Hz α activity mixed with a moderate amount of 6-7 Hz θ activity. Frequent intermittent SWC were recorded in both centro-temporo-parietal (CTP) regions independently and synchronously, showing predominance to the left side during wakefulness, which became almost continuous, diffuse SWC at 2 Hz during sleep. She repeatedly dropped her left arm (ENMlt), and at times, both arms synchronously and symmetrically (ENMbil), when asked to outstretch both arms in front of herself *(figure 1)*. On several occasions, she fell backwards immediately when she dropped both arms symmetrically whilst either sitting or standing *(figure 1)*. A total of 17 seizures including seven ENMlt, five ENMbil, and five drop attacks without significant artifacts were captured for analysis. The ongoing surface EMG of both deltoid muscles was interrupted suddenly for 187 ± 52 ms (n = 7) at ENMlt, 184 ± 30 ms at ENMbil (n = 5), and 276 ± 48 ms at drop attacks (n = 5), respectively *(figure 2)*. The duration of ENM was significantly longer for drop attacks than ENMlt and ENMbil ($p < 0.05$). All seizures were time-locked to SWC and arose from both CTP areas. The latency between the negative spike peak of SWC and EMG trigger points of ENMlt, ENMbil, and drop attacks reached 68 ms, 42 ms, and 8 ms, respectively *(figure 2)*. Thus, the onset of EMG silent period associated with drop attacks and ENMbil preceded that of the slow-wave component of SWC. The height of the spike as well as the slow-wave component of SWC for drop attacks was significantly larger ($p < 0.05$) than that for both ENMlt and ENMbil (spike component: 607 ± 101, 145 ± 49 and 327 ± 162 μv, respectively; slow wave component: 535 ± 49, 284 ± 63 and 332 ± 116 μv, respectively).

ENMlt
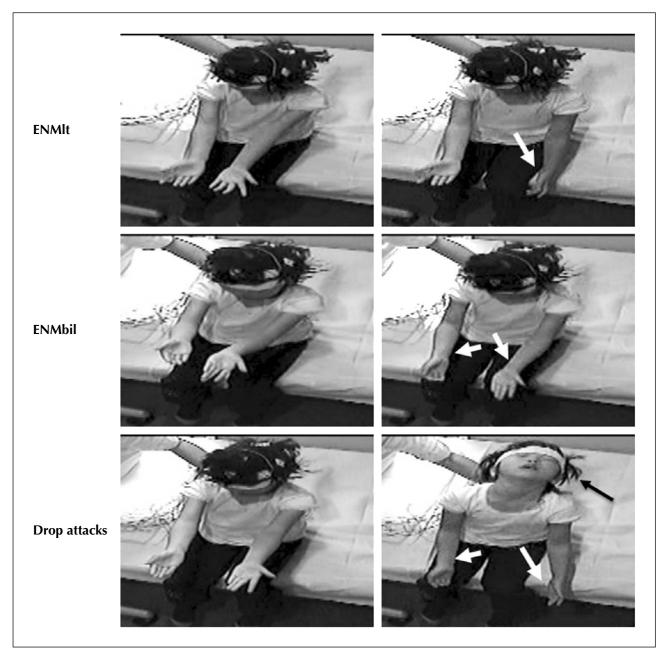
ENMbil

Drop attacks

Figure 1. Video recordings of epileptic negative myoclonus (ENM) and drop attacks. The patient was sitting and asked to outstretch both arms in front of herself; sudden dropping of the left arm was frequently observed (ENMlt). Occasionally, both arms were dropped synchronously and symmetrically (ENMbil), sometimes whilst falling backwards, requiring support of the trunk.

The girl was diagnosed with ABPE and CBZ treatment was immediately discontinued and treatment with ethosuximide (ESM) initiated. The EEG markedly improved, and she remained seizure-free from this point onwards. At six years and nine months of age, the Wechsler Intelligence Scale for Children (WISC-III) showed full intelligence quotient (FIQ) of 95, verbal intelligence quotient (VIQ) of 94, and performance intelligence quotient (PIQ) of 97.

Discussion

Since the precise seizure characteristics of drop attacks have not been investigated for ABPE, it is difficult to compare the semiological and neurophysiological differences between those of ABPE and LGS or MAE. Several ictal polygraphic studies of patients with ABPE demonstrated that ENM involving the arms or legs, as well as atypical
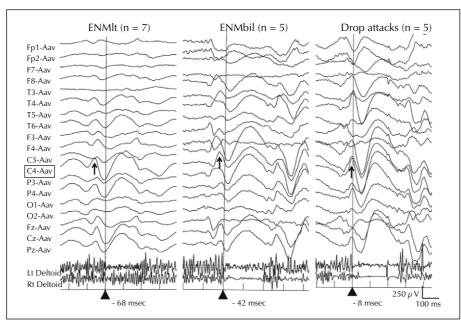
Figure 2. Average simultaneous EEG recordings corresponding to Figure 1. Averaged EEGs showed brief interruption of ongoing EMG activity time-locked to focal spike-and-wave complexes (SWC) from both centro-temporo-parietal (CTP) regions. The mean latencies between the onset of SWC at electrode C4 (↑) and that of ENM and drop attacks (▲) reached 68 ms for ENMlt, 42 ms for ENMbil, and 8 ms for drop attacks, respectively. In addition, the height of the spike as well as the slow-wave component of SWC at electrode C4 in drop attacks was significantly higher than that for both ENMlt and ENMbil (p < 0.05). ▲ indicates the trigger point.

absence seizures, are primary seizure types of ABPE. A precise computer-assisted back-averaging study showed that ENM involving either the arms or legs was time-locked to the contralateral CTP or vertex SWC, with a latency ranging approximately from 15 to 50 ms (Tassinari *et al.* 1995, Capovilla *et al.* 2000, Meletti *et al.* 2000).

In this study, we demonstrated ENM of the arms and drop attacks corresponding to bilateral CTP-SWC, with the greatest amplitude corresponding to the latter. Despite the limitation of the number of surface EMG recordings, it is presumed, based on the slow motion analysis of drop attacks, that ENM involving not only the deltoid but also axial muscles resulted in falling backwards. Although drop attacks caused by ENM associated with the legs have been reported in patients with ABPE, the girl dropped to the floor when either sitting or standing. Thus, drop attacks associated with ABPE can be considered to be the result of more wide-reaching ENM events. The latency between the onset of SWC and drop attacks was much shorter than that of ENMlt and ENMbil (8 ms *vs* 68 ms, 42 ms, respectively), and the amplitude of the corresponding SWC (both spike and slow-wave components) was higher for drop attacks than for ENMlt and ENMbil. Speculation remains as to the neurophysiological mechanism underlying ENM, although, two hypotheses have been postulated, based on: 1) the involvement of a negative motor area producing focal atonia, and 2) direct post-excitatory inhibition of the sensory-motor cortex of a

given somatotopic area (Tassinari *et al.* 1995, Rubboli *et al.* 2006, Oguni *et al.* 1992, 1998). If the latter is true, drop attacks were simply caused by the involvement of a wider somatotopic area, i.e., from the arm area to the adjacent truncal area, positioned side by side. The shorter latency of drop attacks, with onset preceded by larger SWC, may have been caused by a more powerful inhibitory mechanism interrupting sustained axial muscular contractions. However, the onset of EMG silent period associated with drop attacks and ENMbil was shown to precede that of the slow-wave component of SWC, which contradicts the hypothesis that ENM is simply generated by intracortical inhibition represented by the slow-wave component. The latency of 8 ms from the right central head region to the left deltoid muscle in drop attacks strongly suggested the activation of corticospinal pathways, since the corresponding latency in adults has been shown to be 10.8 ms (Ikeda *et al.* 2000). Ikeda *et al.* (2000) studied silent period responses by direct cortical stimulation of the primary sensory-motor area in humans, and speculated that the initial part of the silent period (up to 50 ms) is caused by inhibitory interneurons in the spinal cord produced by excitatory corticospinal pathways, while the latter part is generated by an intracortical inhibitory mechanism. Thus, it is suggested that SWC in drop attacks were strong enough to involve an initial spinal mechanism, while those in both ENMlt and ENMbil could not activate corticospinal pathways, leading to the lack of the initial part of the silent period (ENM), resulting

in longer latencies than drop attacks (Ikeda *et al.* 2000). In other words, ENM, if strong, would be generated initially by the spike-related rather than slow-wave-related mechanism (Rubboli *et al.* 1995).

ENM is resistant to antiepileptic drugs that are effective against focal epilepsy but is sensitive to ESM, exhibiting a close pharmacological similarity to absence seizures (Oguni *et al.* 1998). As both ENM and drop attacks in this patient also responded very well to ESM, the difference in both seizure types is simply a matter of intensity. Drop attacks for both LGS and MAE have been studied using video-polygraphic recordinds, showing that they are caused typically by generalized tonic flexor and atonic seizures, respectively (Beaumanoir and Blume 2005, Oguni *et al.* 2001). In contrast, drop attacks in ABPE were caused by ENM involving axial muscles corresponding to the bilateral centro-temporo-parietal SW complex. Thus, ENM can produce not only focal but also more global atonia resulting in drop attacks, indicating that drop attacks in ABPE are of focal origin despite the similarity with drop attacks observed in cases of LGS and MAE.

The differentiation of epileptic drop attacks among major epileptic syndromes is important because drop attacks are dangerous, at times causing life-threatening injuries. The response to treatment for drop attacks in ABPE is markedly improved when a proper treatment strategy is introduced, thus differential effects of treatment of drop attacks should be appreciated in order to distinguish diagnosis from LGS and MAE. □

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