

# Late-life absence status epilepticus: a female disorder?

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**ABSTRACT** – We report on three women and a review of the literature on absence status epilepticus over the age of 50 years. Our aim was to characterize the male-female ratio in this condition. Out of 16 studies on absence status epilepticus over the age of 50, including our cases, a female dominance was found in 15. We found altogether, 104 (71%) females and 42 (29%) males. This gender difference is highly significant ( $p < 0.00001$ ). We conclude that absence status epilepticus over the age of 50 is predominantly a female disorder.

**Key words:** epilepsy, absence status, non-convulsive status, late absence

Absence status epilepticus (ASE) manifests clinically as a mental disturbance of varying type and intensity, lasting from 30 minutes to days or weeks. The diagnostic challenge can be easily resolved by an EEG showing permanent generalized 2.5-4 Hz spike-wave activity (Rüegg and Dichter 2003). Diagnosing ASE is easy if an EEG is performed. Hitting upon the idea of absence status epilepticus in elderly patients (ASE-E), however, is not easy, since the typical time for the onset of absence epilepsy is during childhood and adolescence. Absence epilepsy is also under-diagnosed in these age groups (Bauer *et al.* 2007), and ASE may develop *de novo* in adults (Thomas and Andermann 1994).

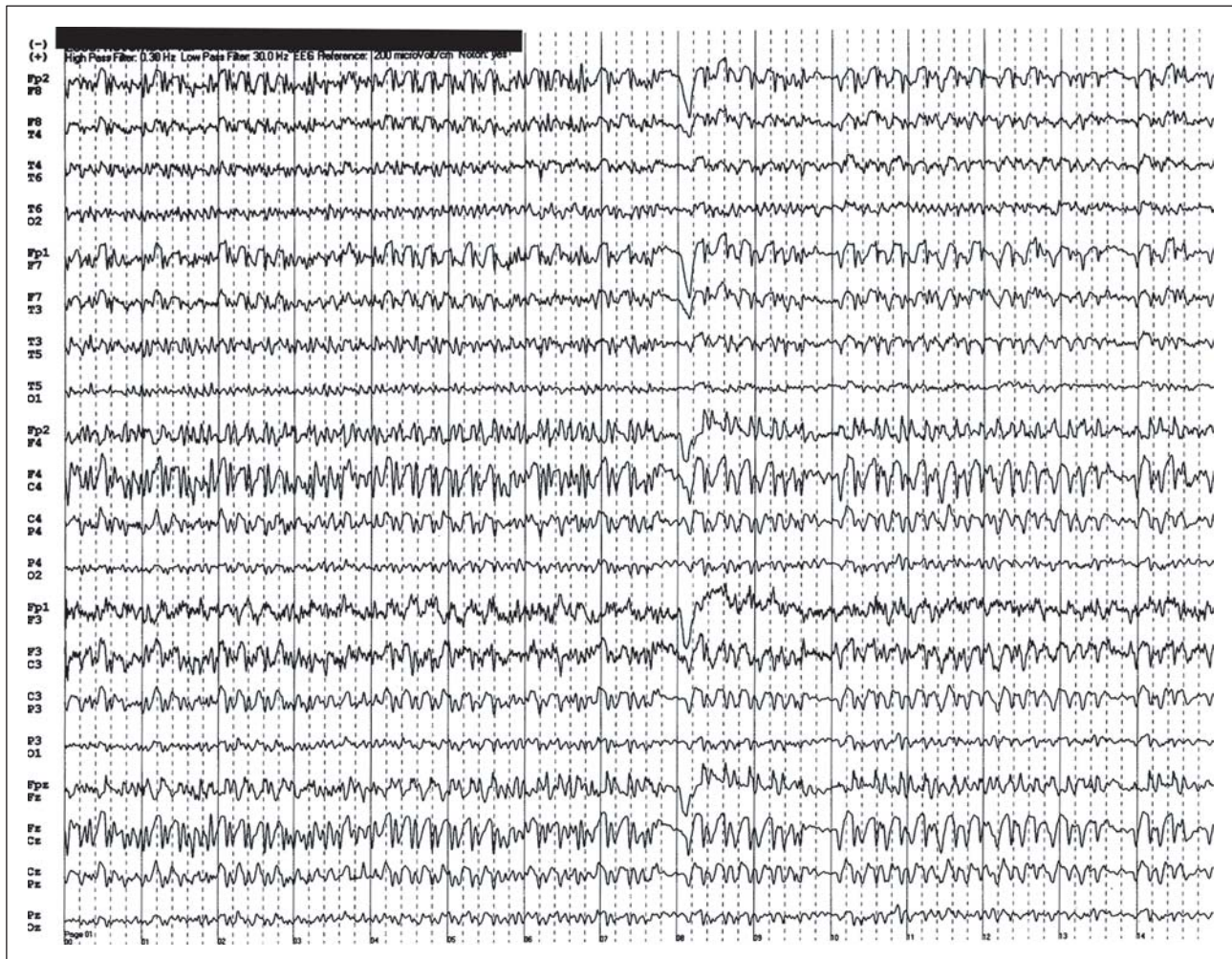
Our three ASE-E patients were all women. Reading the recent paper of Bauer and colleagues on ASE-E, we saw that their four patients were all women as well. We wondered, would the wider literature show ASE-E to be a predominantly female disease?

## Case reports

*Patient 1:* NL, a 56-year-old housewife had probable juvenile absence epilepsy since the age of six. Her generalized tonic-clonic seizures and absences had been treated with phenytoin, carbamazepine, clonazepam and phenobarbital. She had had psychotic episodes and had been hospitalized in psychiatric wards several times. She was referred to our unit on account of sparse, generalized tonic-clonic convulsions as well as frequent “small seizures” with absence-like features. The physical examination showed no abnormalities and her brain MRI was normal. At admission, her movements and speech were unusually slow, she had small, episodic jerks of the jaw and she seemed to be absent, disoriented and strange. The routine EEG showed a continuous 2.5-3.5Hz spike-wave pattern, which disappeared on intravenous diazepam (*figure 1*). Her psy-

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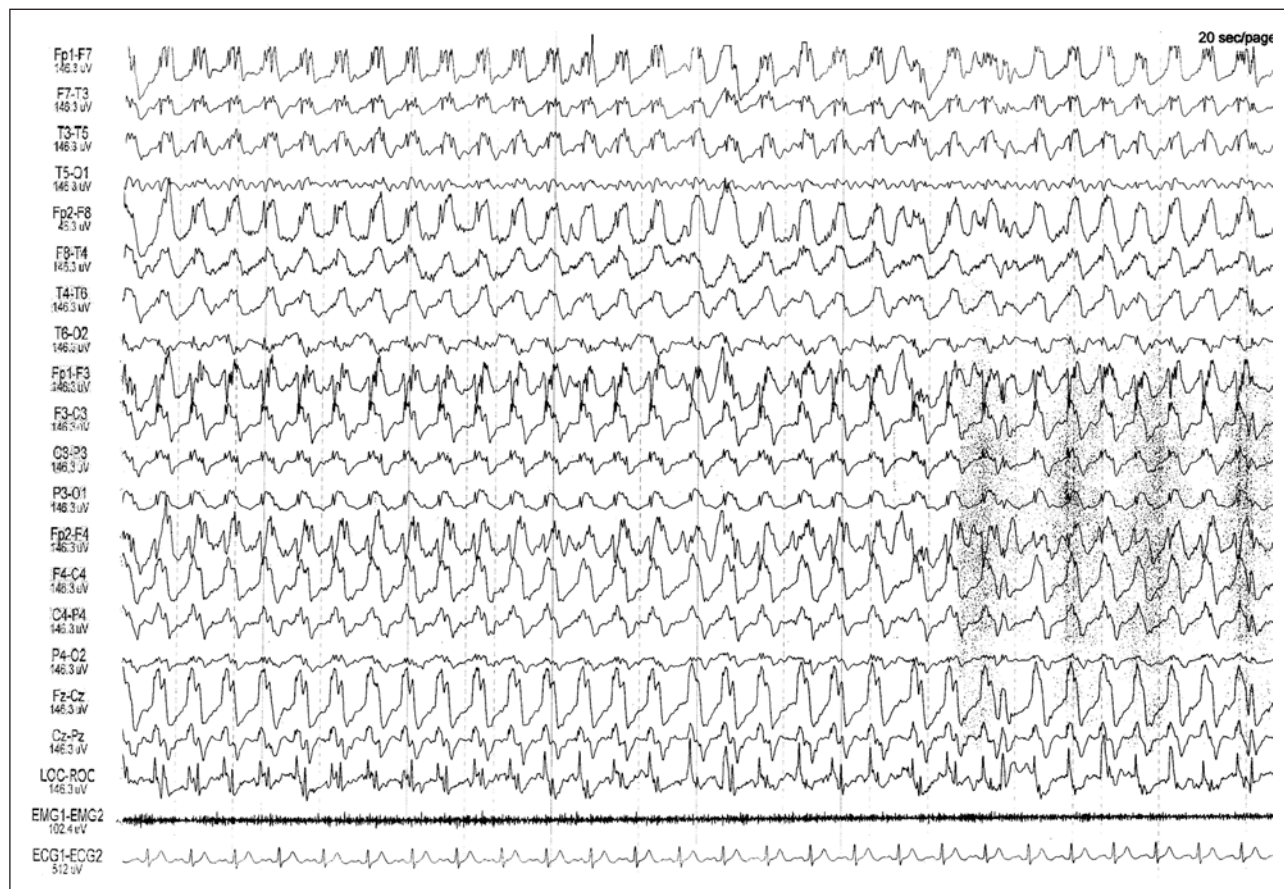
**Figure 1.** Continuous, generalized, 2.5-3.5Hz spike-wave pattern of patient 1, during her slow, confused state.

chomotor activity improved, she became orientated and responsive. We tapered off carbamazepine, assuming a probable paradoxical seizure-aggravating effect in her idiopathic generalized epilepsy and switched to valproic acid. It led to a general slowing of her psychomotor activity as well as the EEG - it turned out to be a valproate-induced hyperammonemic encephalopathy. She became seizure-free on 250mg lamotrigine/day.

**Patient 2:** NJ, a 55-year-old accountant had been treated for probable idiopathic generalized epilepsy for 10 years with carbamazepine and lamotrigine. MRI of the brain was normal. According to information given by her daughter she had had "bigger" convulsive seizures as well as strange states lasting for hours or days. In these states she could not care for herself, was disoriented, could not perform everyday activities, and sometimes became paranoid and aggressive. Then she improved spontaneously and she became active, orientated and cooperative again. A 24-hour EEG was indicated to clarify the diagnosis:

psychogenic states or paroxysmal behavior changes of epileptic origin. At admission, she was extremely slow, smiling, vague and confused. She remembered some of her personal information but answered with a 1-2 minute delay and could not find her bed. One hour later she was orientated with normal psychomotor activity. On her sleep EEG, a continuous 2.5-4Hz spike-wave pattern was seen, which disappeared on intravenous diazepam (figure 2). We tapered off carbamazepine because of a probable paradoxical seizure-aggravating effect and switched to valproic acid; the absence status has not returned. She has been seizure-free for two years.

**Patient 3:** TL, a 63-year-old factory worker was admitted to our center on account of *grand mal* status epilepticus lasting for more than one hour. MRI of the brain showed a severe leukoaraiosis. She had been treated with valproic acid for probable juvenile absence epilepsy since the age of 15 which manifested as two-three generalized tonic-clonic seizures/month and were probably episodes of ASE.



**Figure 2.** Continuous, generalized, 3-4 Hz spike-wave pattern of patient 2, during her slow, disoriented state.

She had compliance problems as at admission, the blood level of valproic acid was 0. After intravenous administration of clonazepam her convulsive seizures stopped, but she remained in stupor, with no verbal or meta-communicative contact and she stared in a rigid, vague way. She sat or lay and remained in forced positions in a catatonic manner. The EEG showed a continuous 3 Hz spike-wave pattern, which disappeared after 10 mg intravenous diazepam her stupor resolving as well (*figure 3*). Sodium valproate (900 mg/d) was administered. The ASE has not returned. Her case seems to correspond to the transformation of generalized convulsive status epilepticus to non-convulsive status epilepticus.

## Methods

We performed a review of the literature looking for the gender distribution of published cases on ASE-E. The cases analyzed included both idiopathic epilepsy cases manifesting in the earlier years of life and late onset - *de novo* - absence status cases. We chose patients over 50 years of age, following the method of Thomas and Andermann described in 1994.

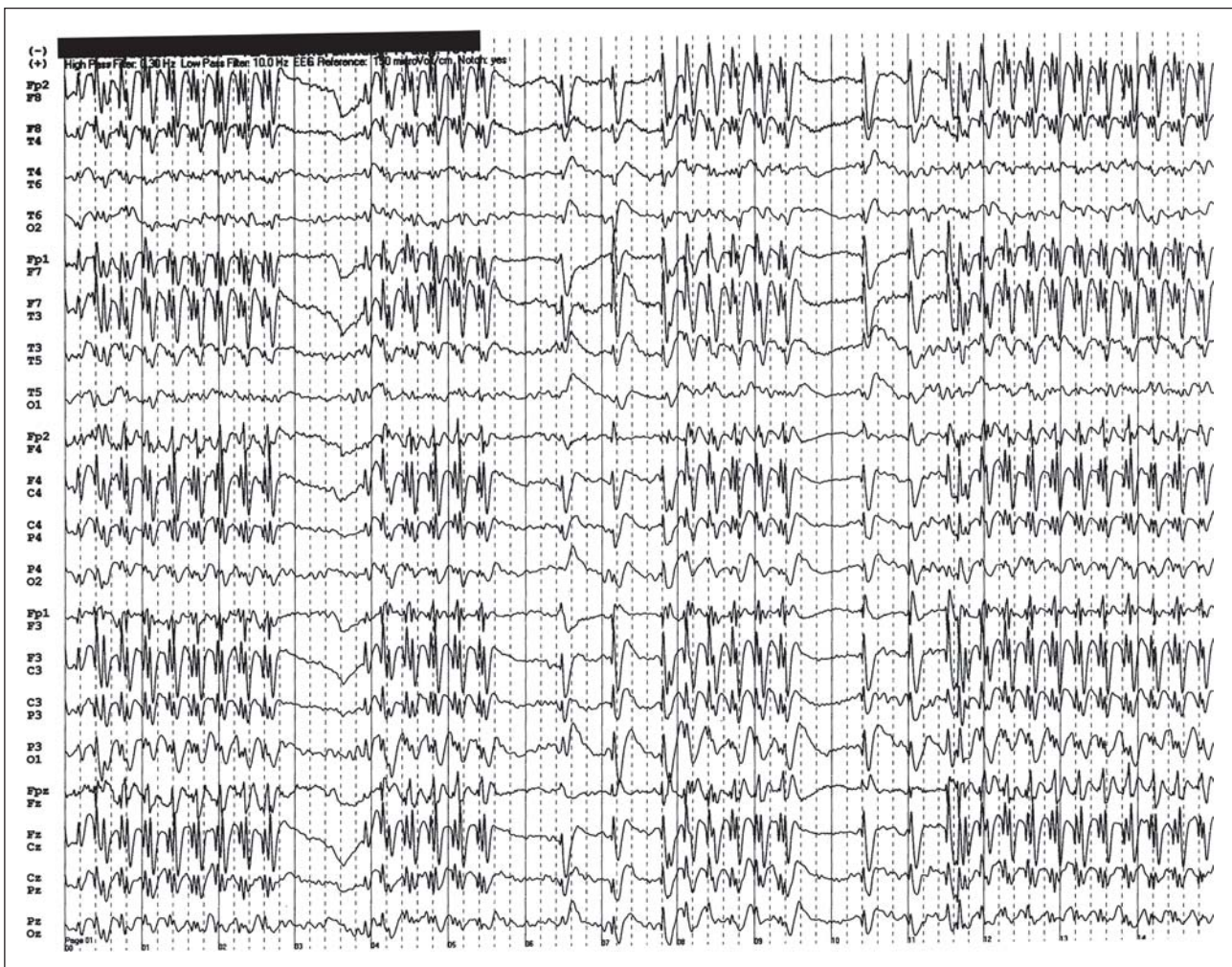
## Results

Out of 16 studies on ASE-E, a female dominance was found in 15. We found altogether 104 females (71%) and 42 (29%) males. Using a binomial test, this gender difference is highly significant:  $p < 0.00001$  (*table 1*).

## Discussion

Gastaut observed that "primary generalized epilepsy in old age is... almost exclusively represented by perimenopausal women..." (Thomas and Andermann 1994). In the ASE-E series (50-90 years) of Thomas and Andermann, 72% were women. To our knowledge however, ASE-E has not been studied systematically for gender differences. Our analysis shows that ASE-E - independently of its type and precipitating factors - seems to be a predominantly female condition.

Epilepsy in general (Sillanpää *et al.* 2006), and especially idiopathic generalized epilepsy, shows slight female dominance - 59% females *versus* 41% males - in every age group (Christensen *et al.* 2005). The incidence of any status epi-



**Figure 3.** Continuous, generalized, 2.5-4Hz spike-, polyspike and wave pattern during patient 3's stuporous state.

lepticus increases in the elderly (Hesdorffer *et al.* 1998, Knake *et al.* 2001 Coeytaux *et al.* 2000), and also any type of non-convulsive status epilepticus seems to develop more easily in elderly women than in elderly men (Towne *et al.* 2000, Shneker and Fountain 2003). The strong female dominance of ASE-E found however, greatly exceeds these ratios. The origin of this gender difference remains speculative.

The theoretical possibilities are as follows:

- the longer life expectancy (2-5 years) of women than men (Health, US Department 2006) may contribute, but not fully explain, the high gender difference found;
- women seek medical help more readily; however, ASE is usually an emergency condition, so this cannot explain our finding;
- there may be a biological background for the female dominance.

It has been suggested that the development of ASE-E may depend on factors different from those influencing

absence epilepsies in general; ASE-E is entirely different from absence status occurring in childhood (Thomas and Andermann 1994, Gibberd 1972, Ellis and Lee 1978, Dunne *et al.* 1987). Thomas and colleagues suggest that "late-onset absence status epilepticus is most often situation-related" - the main precipitating factors being psychotropic drugs, especially benzodiazepine withdrawal, which can trigger ASE-E. The situation-related character of ASE-E however, does not explain the gender difference found. One of the fields of possible interest might be the effect of female sex hormones. The age profile of absence epilepsy shows a clear pattern, suggesting the effect of female sex hormones: in childhood absence epilepsy, the female/male ratio = 63/37 (not statistically significant); in juvenile absence epilepsy (ratio = 76/24) this difference becomes more marked and it decreases again later in life (Christensen *et al.* 2005). ASE-E does not seem to follow this age-profile, preserving the high female preponderance in the elderly. This makes an important

**Table 1.** Reports from the literature on late life absence status.

	Female	Male	Note
Niedermeyer <i>et al.</i> 1979	1	0	
Nightingale and Welch 1982	1	0	
Thomas <i>et al.</i> 1987	10	1	
Berkovic <i>et al.</i> 1989	6	4	
Thomas and Andermann 1994	18	7	
Thomas and Andermann 1994	41	25	Review of the literature on later-life, <i>de novo</i> absence status - some younger (< 50 years) cases included
Primavera <i>et al.</i> 1994	4	1	
Kanemoto <i>et al.</i> 1998	0	1	1.5-2 Hz slow spike-wave status after benzodiazepine deprivation
Pollock and Mitchell 2000	1	0	
Fernández Torre 2001	1	0	2-2.5Hz spike-wave
Dziewas <i>et al.</i> 2002	1	0	Myoclonic absence case
Martin Y <i>et al.</i> 2004	10	3	
Fernández Torre and Díaz-Castroverde 2004	2	0	In addition, they report + 2 female patients with atypical absence status
Narayanan <i>et al.</i> 2007	1	0	
Bauer <i>et al.</i> 2007	4	0	
Our patients	3	0	

role for female sex hormones/ menopausal hormonal changes improbable. The contradictory data on seizure frequency seen in menopausal women also make such an effect improbable (Harder 2005, Harden 1999; Crawford 2005). We suggest that the development of ASE-E might be independent of hormonal effects, and there might be some other - genetic, pharmacological or socially- provoking factors related to the female gender. □

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