Clinical Case Reports International

Case Report
Published: 16 Feb, 2023

Effectiveness of Carbamazepine in Refractory Secondary Enuresis: Case Report

Elena A[1], Francesca S[2], Antonella B[3] and Cristina Z[4]*

[1]Department of Urology, General Hospital Dolo, Venice, Italy

[2]Department of Medical, General Hospital Dolo, Venice, Italy

[3]Department of Pharmaceutical and Pharmacological Sciences, University of Padua, Italy

[4]Department of Neurology, General Hospital Mirano, Venice, Italy

Case Presentation

A 42-year-old woman with secondary Enuresis (EnS) presented to our outpatient clinics, referred by neurology colleagues. Anamnestically, she reported 4 miscarriages, 2 stillbirths, and previous cholecystectomy for stones. The EnS had started at the age of 20 years. At 22 years of age, the patient had performed an Electroencephalogram (EEG) following a generalized tonic-clonic seizure, which showed the presence of modest irritative signs with diffuse projection prevailing over the anterior regions; marked tendency to drowsiness was also reported on that occasion. These EEG changes persisted for about 20 days and then disappeared in subsequent control tracings. At the time she was placed on antiepileptic treatment with Carbamazepine (CBZ) 200 mg 3 times/day, continued for 7 years. During drug treatment the EnS disappeared to reappear upon discontinuation of CBZ.

The patient then performed neurologic re-evaluation and Nuclear Magnetic Resonance Imaging of the brain, both of which were negative. A subsequent video-EEG was normal except documenting an episode of enuresis upon reaching stage 1 of non-REM sleep and failure to reach the deeper stages of sleep. Epileptic genesis of the enuresis was therefore ruled out. Various antimuscarinics and Amitriptyline were prescribed sequentially, all of which were ineffective on enuresis.

When the patient came to our observation, she reported stably using nighttime diapers. The 4-day bladder diaries documented constant enuresis (350 cc to 550 cc by wipe weighing) and 4 to 5 daytime voiding's with average bladder capacity about 250 cc and average micturition urgency of grade 1.5 (range 0-2) according to the "Patient's Perception of Intensity of Urgency Scale" (PPIUS), which describes the degree of micturition urgency on a scale from 0 (no urgency) to 4 (urge urinary incontinence) [1]. Post-void residual was not detected. On urodynamic study, reduced cytometric maximal bladder capacity was detected, and the micturition phase occurred with detrusor contraction (Figure 1, 2). Normality of anemia, plasma and urinary osmolarity excluded possible endocrine causes of enuresis such as diabetes insipidus or syndrome of inappropriate secretion of anti-diuretic hormone. Thus, a picture of overactive bladder [2] associated with sleep disturbance was diagnosed.

All proposed behavioral and pharmacological treatments (reduced evening water intake, desmopressin, night alarm, antimuscarinics such as oxybutynin and solifenacin, mirabegron) were ineffective even in combination. Therefore, the patient resumed low-dose CBZ intake (200 mg/day), with significant reduction of enuresis episodes (1 wet night every 9-10), with no changes in bladder diaries and in post-void residual. During treatment anemia, urinary osmolality and serum osmolality remained in the normal range. After 6 months, the patient preferred to discontinue therapy due to side effects such as sensory dulling and drowsiness.

Discussion

Primary nocturnal enuresis (EnP), a common condition that affects 5% to 10% of children up to 7 years of age, appears to depend to varying degrees on 3 factors: bladder dysfunction, nocturnal polyuria, and failure to awaken to the sensation of bladder filling [3]. In EnS, on the other hand, it is believed that the underlying causes of the disorder are predominantly overactive bladder-as reported by Madhu et al. in 201r analysis of 12,795 women undergoing comprehensive evaluation including urodynamic study [4] -or bladder dysfunction associated with sedative drugs use [5] or obesity [6]. There is also believed to be a relationship between some types of focal epilepsy and

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Correspondence:
Elena Andretta, Department of Urology, Dolo General Hospital, Venice, Italy, E-mail: elena.andretta@aulss3.veneto.it

Received Date: *27 Jan 2023*
Accepted Date: *13 Feb 2023*
Published Date: *16 Feb 2023*

Citation:
Elena A, Francesca S, Antonella B, Cristina Z. Effectiveness of Carbamazepine in Refractory Secondary Enuresis: Case Report. Clin Case Rep Int. 2023; 7: 1481.

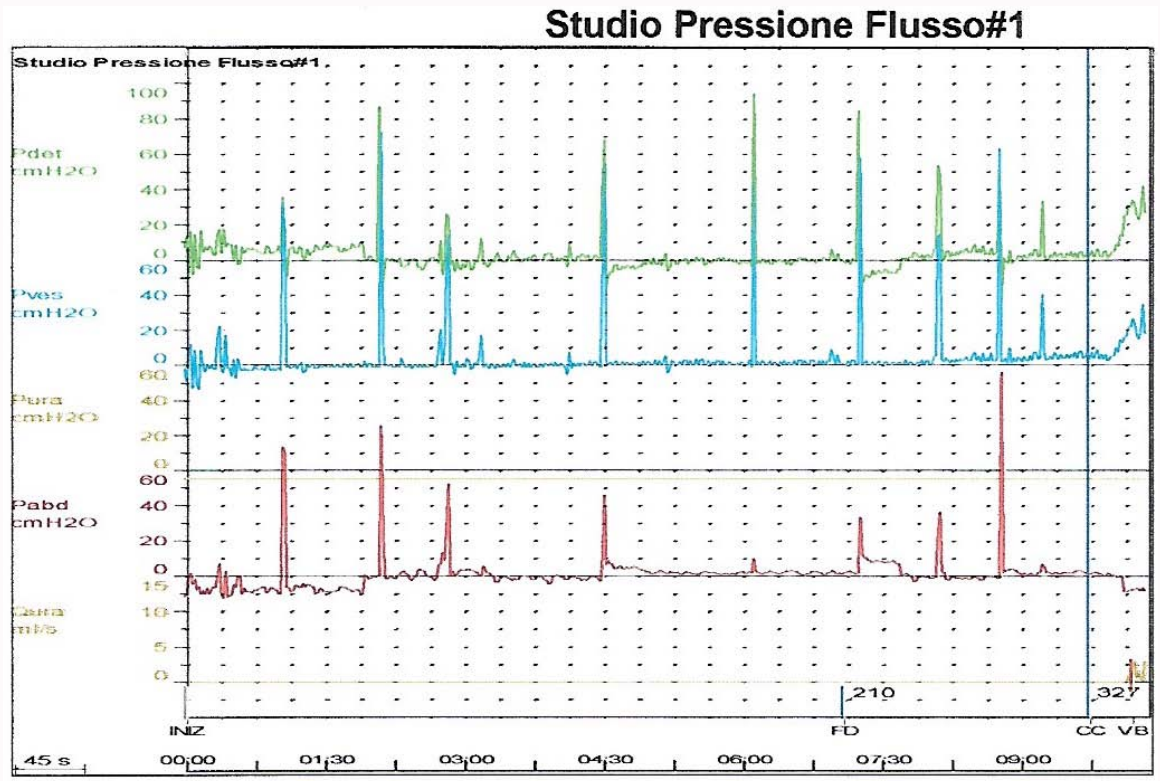

Figure 1: Pressure-flow study, filling phase: the 1st voiding desire is felt at 210 cc and bladder fulness at 327 cc, without comparison of bladder contractions.

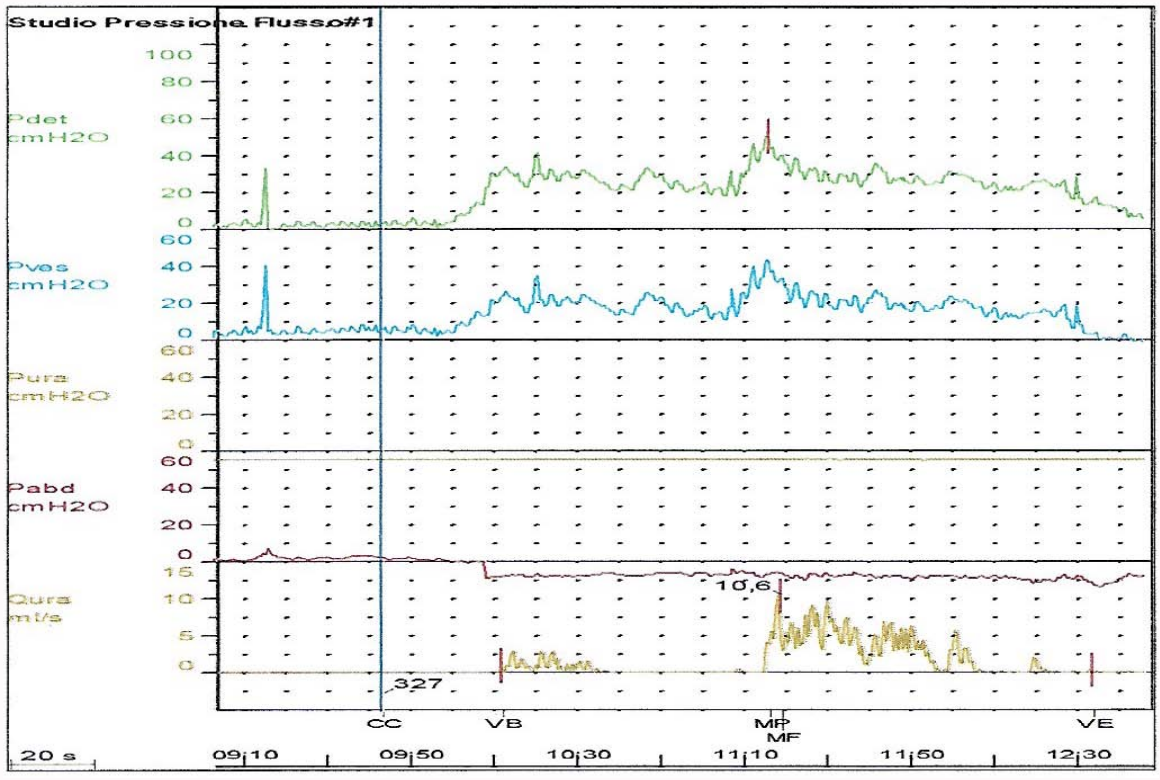

Figure 2: Pressure-flow study: the voiding phase occurs with prolonged bladder contraction at low pressure (30 cm H_2O).

enuresis [7].

Few studies in the literature, most of them quite dated and with unambiguous conclusions, have investigated the possible involvement of sleep disturbances among the pathogenetic mechanisms of EnP. Through polysomnographic recording of 25 enuretic subjects aged 7 to 17 years, Nevéeus et al. showed that enuresis occurred predominantly during non-REM sleep [8], a finding confirmed by other authors [9]. In addition, a systematic review on the possible role of sleep and arousal activation mechanisms in the pathogenesis of enuresis found that enuretics have a higher arousal threshold with deeper sleep [10].

Al-Waili et al. evaluated the use of CBZ in EnP: In a randomized trial of 26 subjects, he found that CBZ 200 mg was significantly effective compared to placebo in the treatment of EnP (mean number of dry nights/months 18.8 ± 8.8 *vs.* 3.9 ± 5.2 with placebo) [11]. In 2006, the same author observed in 8 patients that CBZ produced a marked reduction in daytime and nighttime diuresis and an average increase in 24-h urinary osmolality of 43% [12], suggesting an antidiuretic effect of CBZ.

Another interesting finding regarding CBZ comes from a couple of case-reports in which its prolonged intake had caused chronic urine retention that resolved with discontinuation [13,14]. These cases suggest that CBZ can facilitate urine storage in susceptible people through 2 different mechanisms: The anticholinergic effect with reduction of bladder contractility and the increase of bladder outlet resistance due to hypertone of the internal urethral sphincter.

In the case we described, an epileptic genesis of EnS was ruled out, whereas thanks to Polysomnography, an episode of enuresis was detected during phase 1 of non-REM sleep-that is, the transitional phase from wakefulness to the onset of falling asleep, during which all muscular activity is lost. Therefore, we believe that the causes of EnS in the present case are due to the concomitance of a sleep disorder, with defective awakening mechanisms to the micturition stimulus, and overactive bladder syndrome with good adaptation to bladder symptoms during the waking state. Given that only CBZ has been able to control enuresis, which was refractory to all the treatments included antimuscarinics licensed for overactive bladder, its action on bladder overactivity as well as modulating effect in the central nervous system are conceivable.

Conclusion

In EnS refractory to conventional treatments, CBZ may be a viable therapeutic option probably mainly due to its anticholinergic effect on bladder contraction. However, CBZ is not tolerated by all subjects and its use necessitates careful clinical and biohumoral monitoring (CBZ blood dosage, natremia and liver function).

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