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CASE REPORT

Valproic Acid Induced Sensorineural Hearing Loss; a Case Report of Partially Reversible Hearing Loss In a Patient Treated With Valproic Acid

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Abstract

Valproic acid (VPA) is a frequently used anti-epileptic drug with several common neurological side-effects. Ototoxicity is a less frequent, but serious side effect. We describe a 34-year-old woman with mental retardation and congenital microcephaly of unknown etiology who was treated with VPA for several years because of epileptic seizures. Hearing loss was reported after she started using VPA. The audiogram showed mild to moderate sensorineural hearing loss (SNHL). After replacing VPA by levetiracetam the hearing loss resolved partially. VPA induced reversible sensorineural hearing has previously been described in five patients. All patients had prior hearing loss and therefore this is suggested to be a risk factor for VPA induced SNHL. GABA and sodium channels are suspected to be involved, as SNHL is also described in carbamazepine, gabapentin and vigabatrin. VPA is one of the most commonly used AED's but only five cases have been described. We assume the actual incidence of VPA induced sensorineural hearing loss may be underreported. It is recommended to ask for the existence of hearing loss before VPA is prescribed, since pre-existent hearing loss seems to be an important risk factor. Further research is needed for better understanding of VPA related ototoxicity.

Keywords: Valproic acid; Anti-epileptic drugs; Sensorineural hearing loss; Ototoxity

Abbreviatons:VPA (Valproic acid), AED (anti-epileptic drug), SNHL (sensorineural hearing loss), EEG: (electro-encephalogram), GABA: (gamma-aminobutyric acid)

Introduction

Valproic acid is a frequently used anti-epileptic drug. Common neurological side effects are tremor, cognitive disturbances and Parkinsonism [1]. There are a few reports of (reversible) hearing loss. We report a case of partially reversible hearing loss in a patient receiving VPA [2].

Case description

A 34-year-old woman known with mental retardation and congenital microcephaly of unknown etiology was treated with VPA for several years because of epileptic seizures. She had her first seizure at the age of 24. The seizures were described as tonic seizures. Interictal EEG showed no abnormalities. Neurological examination showed no signs of spasticity. Except for the microcephaly there were no dysmorphic features. She was born in former Yugoslavia. There was no consanguinity. She had one healthy brother. In her family there were no hearing disorders other than presbyacusis. The patient's mother had never noticed hearing impairment during her childhood.

The initial dose of VPA was 2dd 300 mg, but over the years it was gradually titrated up to 1300 mg daily to control seizures. Because of high level plasma concentration (VPA 135 mg/l: N: 50-120 mg/l) it was slightly lowered to 1000 mg daily. No other drugs were taken.

The patient's mother reported that the hearing loss began after the patient started using valproic acid. She was referred to a specialized audiologic center for further analysis. ENT examination showed no abnormalities. The first audiogram was performed at the age of 31. It showed a moderate SNHL. Fletcher indexes were AD 45dB (H) and AS 42dB (H). Bone conduction was similar to air conduction levels, hearing aids were provided.

Valproic acid was replaced by levetiracetam because of the hearing loss. Seizure control remained good. In the months after stopping valproic acid she reported a partial improvement of the hearing loss. A minimal gain in hearing was confirmed (as shown in Figure 1 & 2), mainly in the high frequencies, by audiometry. Fletcher indexes were AD: 35 dB (H) AS: 42 dB (H). Hearing aids were however still needed.

Discussion

Ototoxicity is reported in over 130 drugs and chemicals.

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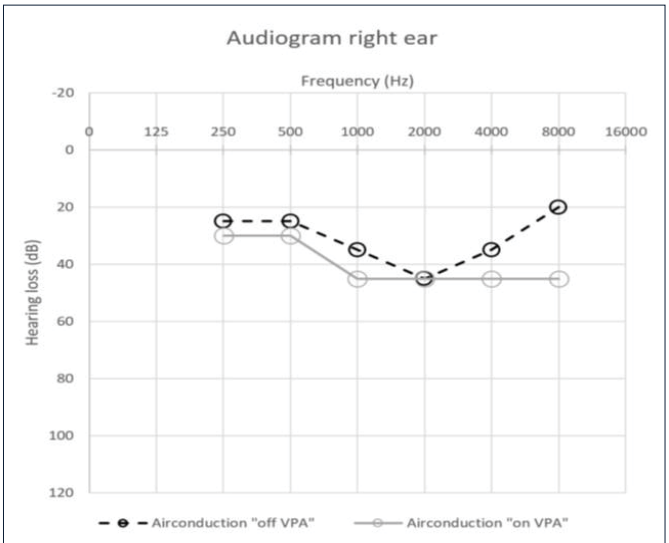

Figure 1: "Audiogram right ear".

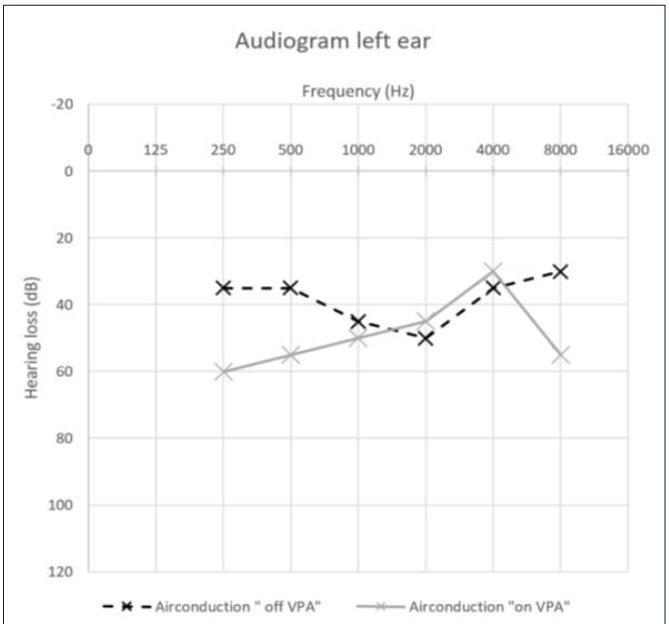

Figure 2: "Audiogram left ear".

Aminoglycosides, loop diuretics, cytotoxic drugs and NSAID's are well known for this. Anticonvulsive agents are also known to cause audiovestibular side effects, mostly dizziness [3]. However audiologic side effects, such as disturbed pitch perception and SNHL, can also occur [4].

Valproic-acid induced reversible sensorineural hearing loss was first described in 1990 by Armon et al [5]. Subsequently, a few other patients were described in case reports [2,6]. Yeap et al described a 39-year-old patient with reversible hearing loss due to VPA which was confirmed after a re-challenge of VPA.

Apart from VPA, there are some other anti-epileptic drugs that are associated with (reversible) hearing loss: carbamazepine, gabapentin and vigabatrin [7–9]. These drugs share a common mechanism of action, which suggests a possible role of GABA, which acts as an important inhibitory neurotransmitter for cochlear inner and outer hair cells. As the other main site of action of VPA is the voltage gated sodium (Na+) channels, it may interfere with the high frequency repetitive firing of Na+ dependent action potentials of the hair cells of the cochlea, auditory nerve and the brainstem auditory pathway. VPA does not seem to affect the responses of brainstem auditory evoked potentials (BAEP) [10].

As shown in table 1, all patients described with VPA induced SNHL were diagnosed with or were suspected to have pre-existent hearing loss. Other authors suggest pre-existent hearing loss may be a contributing factor [2,5,6]. Incecek et al [11-13] showed in a small case series that not all patients are vulnerable for the ototoxic effects of VPA. In 21 pediatric patients without prior hearing deficit they found no alterations of hearing thresholds.

In our patient there was no known pre-existent hearing loss. However, it had never been tested. BAEP was not performed in our patient. A possible relation with an unknown underlying medical condition (causing the mental retardation and microcephaly) could be hypothesized. Congenital cytomegalovirus (CMV) infection is a common cause of bilateral hearing loss in children. The CMV status was not known in our patient [14-16]. Delayed SNHL is described in congenital cases. Progressive hearing loss is also reported.

Author	Patient	Pre-existent hearing loss	VPA dose	Plasma concentration	Recovery
Armon 1990	1) 73 year (M)	Presbyacusis (probable)	3000 mg/d	111,6 µg/ml	10 weeks
	2) 71 year (M)	Yes, AS (due to Janetta)	2000 mg/d	125 µg/ml	AS partial
	* one additional case of a 67 year old man is mentioned but not reported in the paper				
Hori 2003	1) 9 year (F)	Bilateral congenital	100 mg/d	21 µg/dl	Partial (2 months)
	2) 20 year (F) only tinnitus. No hearing loss	No	800 mg/d	59,4 g/dl	Completely
Yeap 2007	39 year (M)	Clinically none, but BAEP was suggestive of conduction defect between cochlear and superior olivary nucleus	800 mg/d	-	3 hours

Table 1: Case reports of patients with VPA induced SNHL.

The clinical features of our patient did not match mitochondrial or syndromic disorders known to cause hearing loss, for example like SPATA5 mutations [17]. Several types of Connexin mutations (GJB2, GJB6) are frequently involved in autosomal recessive nonsyndromic hearing loss; these patients usually have profound SNHL which is noticed at an early age [15,18,19]. Genetic testing was not performed in our patient.

Many ototoxic drugs (like cisplatin and aminoglycoside) affect the hearing thresholds in the higher frequencies (> 8000 Hz) because they preferentially affect the outer hair cells at the base of the cochlea basal region of cochlear outer hair cells. Not all ototoxic agents have this preference. The mechanism of VPA related ototoxicty is not known, therefore it is unknown which region of the cochlear hair cells is affected. In our patient it is remarkable that we see an improvement of 25 dB at 8000 Hz [18-20].

Valproic acid is one of the most commonly used AED's, yet only five similar cases have been described. We assume that the actual incidence of valproic sensorineural hearing loss may be underreported. If VPA affects the higher frequencies specifically (>8000 Hz), it is likely that the hearing loss is not always noticed because the higher frequencies are not related to diminished speech recognition. Only audiometry of the high frequencies will detect the SNHL when it is mild.

Conclusion

SNHL is a serious side effect of VPA which is probably underreported. The pathophysiology is not known exactly, however it is recommended to ask for the existence of hearing loss before VPA is prescribed, as pre-existent hearing loss seems to be an important risk factor. Further research is needed for better understanding of VPA related ototoxicity and to determine the actual incidence.

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