Pyridoxine Dependent Epilepsy with Iatrogenic Sensory Neuronopathy

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ABSTRACT: An 18-year-old man was treated from birth with chronic high dose pyridoxine (vitamin B_6) up to 2000 mg per day for pyridoxine-dependent seizures. Within two years of onset of treatment, he developed a sensory neuropathy which did not progress over the following 16 years. Electrophysiological studies were consistent with a pure sensory neuronopathy expressed as centripetal degeneration of processes of the dorsal root ganglion cells.

RÉSUMÉ: Épilepsie résistante a la pyridoxine avec neuropathie sensitive iatrogénique. Nous présentons le cas d'un homme de 18 ans traité de façon chronique depuis sa naissance par des doses élevées de pyridoxine (vitamine B_6), jusqu'à 2000 mg par jour, pour une épilepsie résistante à la pyridoxine. En moins de deux ans du début du traitement, il a développé une neuropathie sensitive qui n'a pas progressé pendant les 16 années suivantes. Les études électrophysiologiques effectuées étaient compatibles avec une neuronopathie sensitive pure qui s'exprimait comme une dégénérescence centripète des prolongements des cellules des ganglions rachidiens.

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We report a patient with pyridoxine-dependent epilepsy who had an 18-year follow-up. In contrast to previous reports, this patient continued to have difficulty controlling seizures despite massive doses of pyridoxine (vitamin B_6). As a result of the pyridoxine therapy he developed a sensory neuropathy, the features of which are described.

Case Report

This 18-year-old, left-handed student of low normal intelligence was assessed for seizures and peripheral neuropathy. He was noted to have generalized twitching in the delivery room which persisted for four hours despite intravenous diazepam until it stopped abruptly following a single dose of pyridoxine 150 mg intravenously. At 15 days, he had another generalized seizure and pyridoxine 50 mg daily was restarted. His sister had died at age 9 days in status epilepticus but did not receive pyridoxine; a paternal cousin had febrile convulsions and a maternal aunt had generalized tonic clonic seizures. At age one year he began having prolonged febrile convulsions lasting 10-60 minutes about once a month followed at 4 years by recurrent afebrile convulsions and at 13 years by partial seizures of temporal lobe origin. These occurred with variable frequency despite increasing pyridoxine to 2000 mg a day and the addition of phenytoin, phenobarbital and mephobarbital. At age 18 years following the addition of carbamazepine, seizures stopped and pyridoxine was decreased to 100 mg daily. EEGs at age 7 and 18 years revealed rare bursts of generalized spike waves and in the latter, left temporal spikes. An MRI at age 18 years showed left mesial temporal sclerosis.

At age two years, it was noted that he did not respond well to pinprick in the feet. Deep tendon reflexes were reduced but present. Nerve conduction studies at that time revealed absent sensory action potentials in the median and ulnar nerves with normal motor conduction. Sural nerve biopsy revealed evidence of a severe, axonal, sensory neuropathy but a muscle biopsy was normal. Examination at age 18 years revealed absent vibration sense in both feet, decreased position sense in the toes, decreased pain and temperature sensation to the midcalf and in the fingers with absent reflexes and flexor plantar responses. He also had a mild gait ataxia without nystagmus. The patient had no subjective complaints related to these findings. Electrophysiological studies revealed normal maximum motor conduction velocities, motor terminal latencies, M-potentials and needle electromyography. However, the sural, superficial peroneal and median sensory nerve action potentials were all absent, although conduction in the more proximal portions of the peripheral nervous system was normal. For example, the dorsal root potentials recorded at the L4-5 level and again at the T12-L1 level, the latter combined with a cord dorsum potential, were normal in size, shape and latency when recorded monopolarly with epidural electrodes in response to supramaximal stimulation of the posterior tibial nerve in the popliteal fossa (Figure). The maximum sensory conduction velocities between the popliteal fossa and L4-5, and the L4-5 and T12-L1 levels were both normal (60.4 and 70.9 m/sec, respectively). The corresponding cortical sensory potential recorded at the vertex with the forehead as reference, was clearly delayed (44.5 msec as against an upper limit of normal of 35 msec).

Discussion

Pyridoxine dependency is a rare cause of generalized seizures in children first reported about 40 years ago.[1] It is an autosomal recessive disorder which typically presents in neonates as generalized seizures or status epilepticus unresponsive to standard antiepileptic drug therapy. However, seizures stop immediately following parenteral pyridoxine (vitamin B_6). Lifelong therapy with pyridoxine is required to prevent seizure

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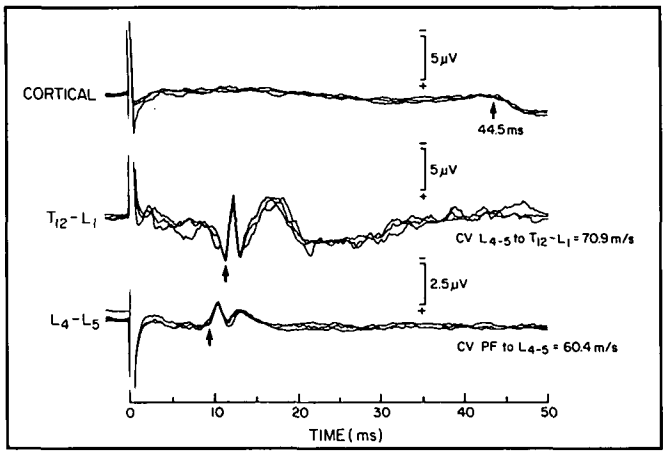

Figure: *Supramaximal stimulation of the posterior tibial nerve in the popliteal fossa and the potentials recorded at the L4-5 and T12-L1 levels with an insulated monopolar electrode inserted into the epidural space. The cortical potential was recorded with surface electrodes located over the vertex and forehead. A clearly-defined dorsal root potential was recorded at both the L4-5 and T12-L1 levels, the latter followed by a well-defined cord dorsum potential.*

recurrence. There has been only one report of long-term follow-up which suggested that the prognosis for complete seizure control is excellent.[2]

Typically, pyridoxine-dependent seizures are completely and permanently controlled by pyridoxine given at doses of less than 100 mg daily.[2] Our patient had not only pyridoxine-dependent seizures but primary generalized and complex partial seizures as well. The presence of the other types of seizures explains why pyridoxine alone failed to provide complete control. Although the family felt that the high dose pyridoxine did decrease the complex partial seizures, their frequency did not change substantially until carbamazepine was added.

Although this is the first report of a sensory neuropathy caused by chronic high dose pyridoxine therapy for seizures, the same type of neuropathy has been reported initially in people on megavitamin diets who took high doses of vitamin B_6[3] and later in patients self-medicating with pyridoxine for other conditions.[4,5] Pyridoxine neuropathy has also been produced experimentally in animals[6] and man.[7] Doses as low as 50 mg/day have been neurotoxic when taken for months or years but most cases have used > 1 g/day. In addition to the neuropathy associated with chronic ingestion of pyridoxine, a severe acute neuropathy has also been described in two patients who received a single massive dose of more than 100 g of parenteral pyridoxine.[8] Thus, the neurotoxic effect of pyridoxine may be cumulative either from a low daily dose over a long time or a high dose over a short time. There also appears to be an individual susceptibility to the neuropathy since some patients do not develop it even after years of therapy.[5] Our patient's neuropathy developed within two years of starting the pyridoxine; however, little or no sign of progression occurred after that despite the continued use of high doses of the vitamin for 16 years. Only a moderate sensory neuropathy was found after 18 years of treatment suggesting that the effect of pyridoxine on the peripheral nervous system is self limited, or related to the magnitude of the initial doses.

Experimental evidence in animals has shown that pyridoxine can induce a distal neuropathy, diffuse axonopathy or a neuronopathy depending on the dose, rate of administration and species studied[6] but the site of the underlying lesion in man has not been clearly demonstrated. The pattern of the electrophysiological abnormalities in this case is most consistent with a centripetal degeneration of processes of the dorsal root ganglion cells caused by a neuronopathy or central distal axonopathy and resulting in a pure sensory neuropathy. This was manifest as abnormal conduction in the distal extremities of both the peripheral and central processes of the dorsal root ganglion cells and preservation of conduction, in the more proximal segments of the peripheral nervous system. The normal amplitude of the dorsal root potential following stimulation of the posterior tibial nerve indicates preservation of the cell bodies within the dorsal root ganglion. As no attempt was made to record ascending sensory activity between the recording sites at the lumbosacral region and cortex, we cannot exclude the possibility of involvement of sensory neurons interposed between the dorsal horn and sensory cortex. Overall, the pattern of sensory abnormalities and the electrophysiological studies in this case are quite in keeping with a pyridoxine-induced toxic sensory neuronopathy, entirely sparing motor neurons.

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