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LETTER TO THE EDITOR

Unexplained epileptic encephalopathy: consider and reconsider pyridoxine dependent seizures

Steven P. Claus [1], Kees P. J. Braun [1], Lambertus Dorland [2], Mireille Bourrez-Swart [3], Onno van Nieuwenhuizen [1], Tom J. de Koning [2]

Departments of [1] Child Neurology, [2] Metabolic Diseases, and [3] Clinical Neurophysiology, Wilhelmina Children's Hospital, University Medical Center of Utrecht, The Netherlands

To The Editor:

The following case history illustrates the diagnostic pitfalls of pyridoxine dependent epilepsy that may lead to serious delay in treatment.

A 5 months old boy was referred to our hospital because of a diffuse encephalopathy with multifocal epilepsy, severe developmental delay and a bipyramidal syndrome. The pregnancy and delivery were uncomplicated. One hour after birth the first seizures were noted with multifocal epileptic activity on the electroencephalogram (EEG). The epileptic activity did not diminish after the intravenous administration of 100 mg pyridoxine shortly after the debut of seizures, and after 300 mg ten days later. Early diagnostic evaluation revealed no infections, nor endocrine or metabolic disturbances. Magnetic resonance imaging (MRI) of the brain was normal. The metabolic analysis included measurement of gama-aminobutyric acid (GABA) and amino acids in cerebrospinal fluid. The child was treated with vigabatrine and phenobarbital successively without satisfactory seizure control.

At admission to our hospital a follow up MRI scan now showed generalized cerebral atrophy. We first started valproic acid without success. Additional treatment with adrenocorticotrope hormone (non-depot ACTH) was then installed. Renewed biochemical and metabolic evaluation showed an elevation of glutamine (1200 micromol/L, normal value 575 ± 105 micromol/L) in the cerebrospinal fluid (CSF). Normally this finding may indicate a urea cycle defect, but this was excluded. We then reconsidered a pyridoxine dependent encephalopathy and started oral suppletion with pyridoxine (15 mg/kg/day) and discontinued valproic acid and ACTH. We observed a rapid remission of the seizures and the epileptic activity on the EEG, as well as an improvement of cognitive and motor function within a week. The glutamine levels in the CSF normalized (480 micromol/L). Subsequent cessation of pyridoxine resulted in a relapse of seizure activity, recurrence of the EEG abnormalities, and deterioration of cognitive and motor development. Reintroduction of the vitamin again reversed these symptoms. This sequence of events clinically confirmed the diagnosis pyridoxine dependent encephalopathy. Contrary to our expectation the glutamine levels had remained normal in CSF samples collected after cessation of the pyridoxine. The earlier elevation of glutamine can best be explained as a side effect of treatment with valproic acid, as has been reported in the literature (1). This coincidental finding, however, led us to the correct diagnosis.

Pyridoxine dependent encephalopathy is a rare disorder (birth incidence 1/157.000), however it is responsive to pyridoxine suppletion (2), which is why the diagnosis must not be missed. The exact biochemical defects still remain to be elucidated, but a disturbance in the GABA pathways is suggested. Until now there is no definite biochemical or genetic marker to prove or exclude the diagnosis. The most frequently relied on test is disappearance of the epileptic abnormalities in the EEG directly after intravenous administration of high dose pyridoxine (up to 300 mg), or hours after oral administration. Elevated CSF glutamate levels, or decreased GABA levels can further support the diagnosis (2,3).

Correspondence: Tom J de Koning, M.D., PhD.,
Department of Pediatric Metabolic Diseases
KC 03.063.0 University Medical Center Utrecht
PO Box 85090, 3508 AB, Utrecht, The Netherlands.
Tel: 00-31-30-2504003, fax: 00-31-30-2505350.
E mail: T.deKoning@wkz.azu.nl
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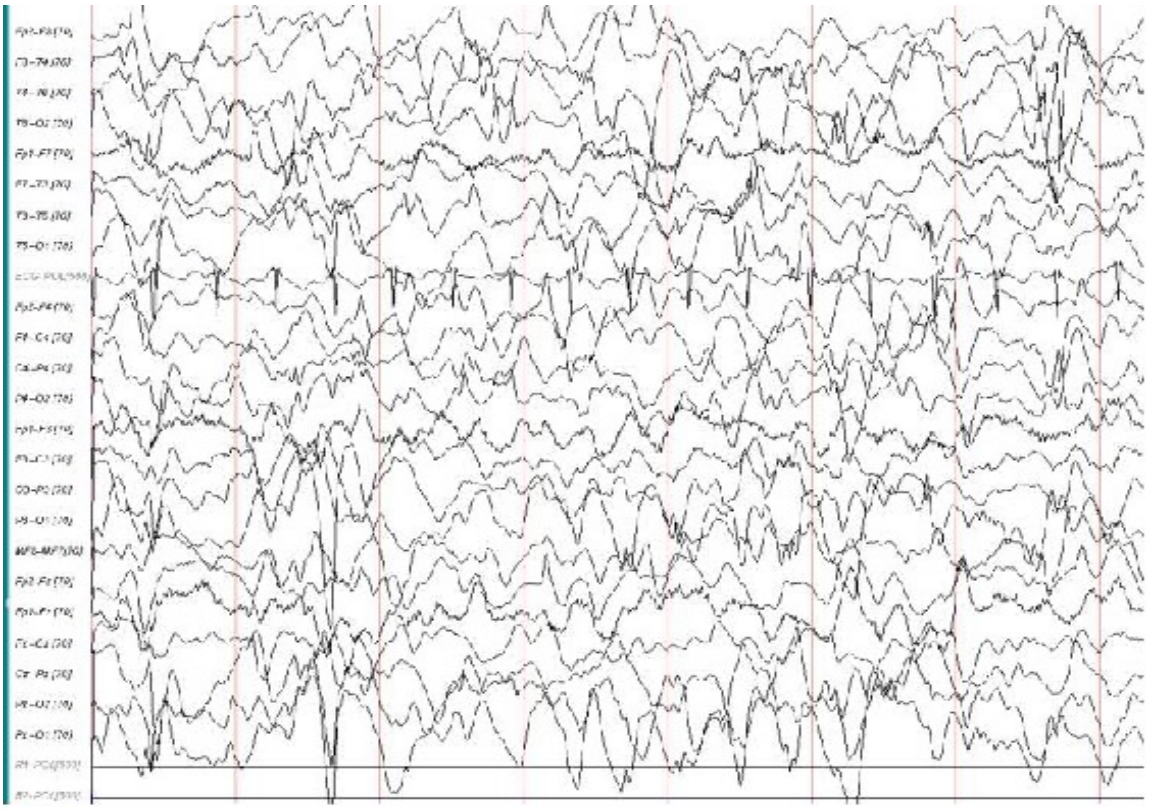

Figure 1. EEG (bipolar montage, sensitivity 70 microV/cm, high frequency filter 70 Hz, low frequency filter 1.0 sec, timebase 1 sec/div) before oral administration of pyridoxine shows hypsarrithmia.

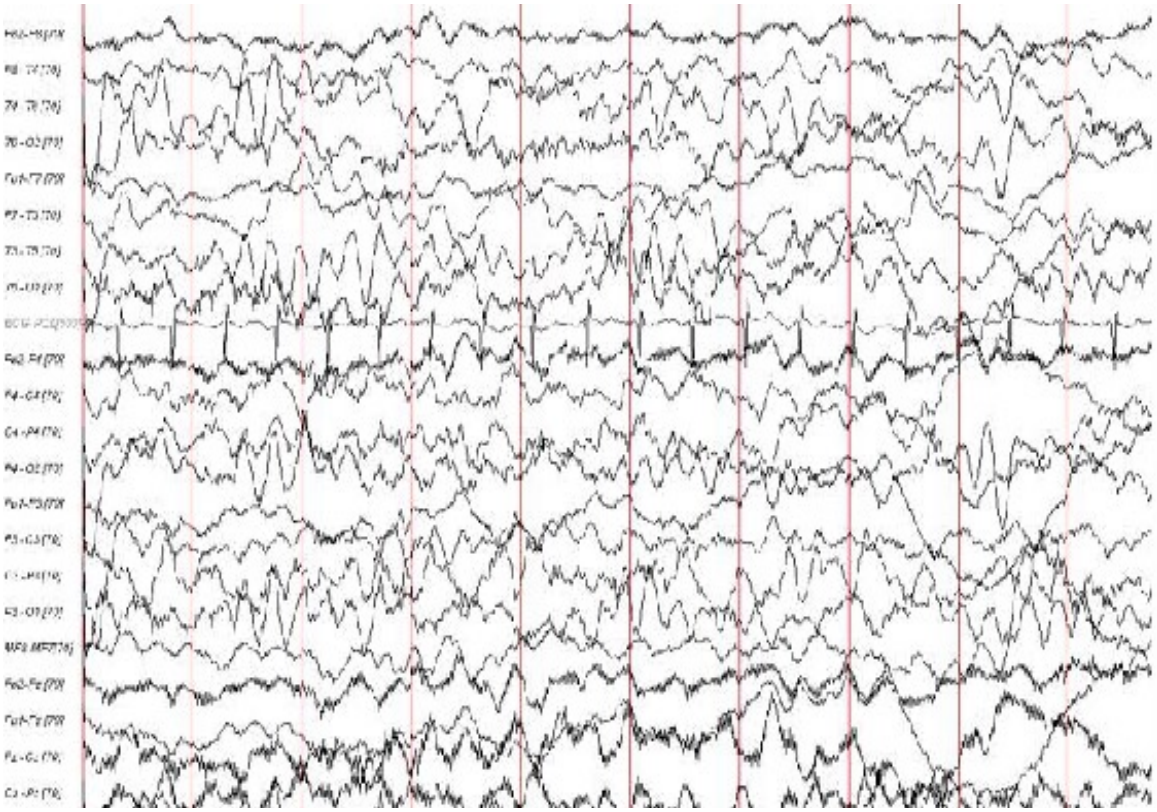

Figure 2. EEG (bipolar montage, sensitivity 70 microV/cm, high frequency filter 70 Hz, low frequency filter 1.0 sec, timebase 1 sec/div) one week after start of oral administration of pyridoxine. It shows a dramatically improved background pattern and no epileptic abnormalities.

Recent epidemiological data indicate that the disorder frequently presents atypically with the absence of an immediate EEG response to pyridoxine administration. Therefore, clinical improvement after continued oral supplementation with pyridoxine and recurrence of symptoms after discontinuation becomes the prerequisites for the diagnosis pyridoxine responsive encephalopathy and not the response to intravenous pyridoxine (3, 4). Treatment with pyridoxine for weeks to months does not carry a high risk of negative side effects. Thus, as already suggested by Goutieres and Aicardi (4) children with an unexplained epileptic encephalopathy deserve a trial of oral pyridoxine suppletion even up to the age of 2 years, to avoid irreversible cerebral damage through unnecessary doctor's delay.

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