Pipecolic Acid: A Diagnostic Marker in Pyridoxine-Dependent Epilepsy

Michèl A. A. P. Willemsen, MD, PhD,[1]
Annelies M. C. Mavinkurve-Groothuis, MD,[1]
Ron A. Wevers, PhD,[2] Jan J. Rotteveel, MD, PhD,[1]
and Cornelis Jakobs, PhD[3]

Pyridoxine-dependent epilepsy (PDE; OMIM 266100) is an autosomal recessive disorder characterized by intractable neonatal seizures responsive only to pyridoxine.[1] The biochemical and genetic backgrounds of PDE have so far not been unravelled. Diagnosis is exclusively clinical and depends on the demonstration of a beneficial effect of pyridoxine. PDE is considered "proven" when seizures recur after pyridoxine withdrawal. Isolated elevations of L-pipecolic acid (PA) have been found in plasma and cerebrospinal fluid (CSF) of three patients with PDE and were considered a possible biochemical hallmark for the disorder.[2]

Our patient is the fourth child of nonconsanguineous parents. The boy was born at 35 weeks of gestation with normal Apgar scores. One hour after birth, onset of seizures and respiratory failure necessitated mechanical ventilation. Electroencephalography (EEG) showed a burst suppression pattern. Treatment with conventional antiepileptic drugs failed. At the age of 4 days, the first dose of pyridoxine (50mg IV) immediately led to an EEG isoelectric. Pyridoxine was continued orally and the boy slowly recovered during the following days. In the first year, spasticity and mental retardation became evident and an obstructive hydrocephalus developed and was surgically treated. Currently aged 6 years, the boy is still receiving pyridoxine and shows moderate developmental delay, spastic dysarthria and gait, but no seizures. EEG shows some slowing of background activity without epileptic discharges. Extensive metabolic workup was performed in the first weeks of life but did not show conclusive abnormalities. Especially amino acids and GABA in CSF were normal. PA, however, was repeatedly demonstrated in urine but never quantified. Recently, we quantified PA in the CSF sample that was taken at age 3 weeks (and had been stored at −80°C) and in freshly taken samples of CSF, blood, and urine (Table). The methods used have been published previously.[3]

Independently, and for the first time after the original publication by Plecko and colleagues[2] in the *Annals* we were able to confirm that elevated concentrations of PA in CSF, and to a lesser degree also in plasma, can be found in PDE. The explanation for the increased concentration of PA and its role in the mechanisms that lead to the epileptic encephalopathy in PDE remains speculative.[2] We consider the demonstration of isolated PA elevations in (suspected) PDE such a strong argument in favor of the diagnosis that the demonstration of isolated PA elevations should prevent patients from dangerous pyridoxine withdrawals.

[1]Department of Pediatric Neurology and [2]Laboratory of Pediatrics and Neurology, University Medical Centre St. Radboud, Nijmegen; and [3]Department of Clinical Chemistry, VU University Medical Centre, Amsterdam, The Netherlands

References

1. Baxter P. Pyridoxine-dependent seizures: a clinical and biochemical conundrum. Biochim Biophys Acta 2003;1647:36–41.
2. Plecko B, Stockler-Ipsiroglu S, Paschke E, et al. Pipecolic acid elevation in plasma and cerebrospinal fluid of two patients with pyridoxine-dependent epilepsy. Ann Neurol 2000;48:121–125.
3. Kok RM, Kaster L, de Jong APJM, et al. Stable isotope dilution analysis of pipecolic acid in cerebrospinal fluid, plasma, urine and amniotic fluid using electron capture negative ion mass fragmentography. Clin Chim Acta 1987;168:143–152.

DOI: 10.1002/ana.20610

Autologous Mesenchymal Stem Cell Transplantation in Stroke Patients

Jacques De Keyser, MD, PhD

Oh Young Bang and colleagues are to be congratulated for their pioneering work on mesenchymal stem cell (MSC) transplantation in stroke patients.[1] However, their statement that we now need double-blind studies with larger cohorts to reach a definitive conclusion regarding the efficacy of this therapy is premature. Evidence that the intravenously administered MSCs were biologically active is indirect and based on a presumed enhanced functional recovery. A major concern in this study is the authors' claim that functional improvement in the transplanted group was better than in the control group.

First, the groups were too small to make such a claim. Second, results were not reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. As such, based on the data in Figure 3, we are confronted with a situation that in the control group (n = 25) patients gradually dropped out at 3, 6, and 12 months. At 12 months, 10 patients in the control group were missing. The reason is not mentioned, but it may greatly influence the interpretation of the results. Third, because there was no sham intervention, it is unclear for me how the assessing neurologist could be blind to the group allocation,

Table. Concentrations (reference values) of Pipecolic Acid in Body Fluids of a Patient with Pyridoxine-Dependent Epilepsy at the Ages of 3 weeks and 6 years

Fluid	3 Weeks	6 Years
CSF	6.99 (0.009–0.12) μmol/L	1.51 (0.009–0.12) μmol/L
Plasma	NA	5.25 and 6.59 (0.54–2.46) μmol/L
Urine	NA	0.07 and 0.10 (0.01–1.54) mmol/mol creatinine

CSF = cerebrospinal fluid; NA = not available.

Published by Wiley-Liss, Inc., through Wiley Subscription Services