A case of extreme prematurity and delayed diagnosis of pyridoxine-dependent epilepsy

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ABSTRACT

يظهر الصرع المعتمد على البيريدوكسين في وقت مبكر من العمر حتى داخل الرحم. لا يستجيب الجسم عادة للأدوية المضادة للصرع ويستجيب فقط إلى تناول البيريدوكسين مدى الحياة، وعادة ما تكون النوبات معممة على كامل الجسم. نستعرض في هذا المقال حالة طفل يبلغ من العمر 3 سنوات، وقد وُلد خديجاً بعد 25 أسبوعاً من الحمل. بدأ يعاني من حركات غير طبيعية في الشهر الثاني من العمر. وأُصيب في الشهر العاشر من العمر بتشنجات صرعية مستمرة لم تستجب إلى العديد من الأدوية المضادة للصرع، وتمت السيطرة عليها باستخدام البيريدوكسين الوريدي. لقد أثبت وجود مستوى مرتفع من إفراز ألفا أمينوديبيك سيمي ألدهيد في البول تشخيص الصرع المعتمد على البيريدوكسين. كما أكد تحليل الطفرة الجينية دقة التشخيص. وتدعو هذه الحالة إلى النظر في الصرع المعتمد على البيريدوكسين ومعالجته في وقت مبكر، وحتى في حالة المواليد الخدج المصابين بمضاعفات عصبية.

Pyridoxine-dependent epilepsy presents early in life, even in utero. It is usually refractory to conventional antiepileptic medications and responds only to lifelong pyridoxine supplementation. Seizures are usually generalized tonic clonic. We report a 3-year-old child that was born prematurely at 25 weeks of gestation. He presented with abnormal movements in the second month of life. At 10 months of age he presented with status epilepticus, which was refractory to multiple antiepileptic medications and was controlled with intravenous pyridoxine. An elevated level of α-aminoadipic semialdehyde excretion in the urine supported the diagnosis of pyridoxine-dependent epilepsy. Subsequently, a c.1195G>C homozygous mutation in the 5q31 aldehyde dehydrogenase 7A1 gene was confirmed. This case calls for considering pyridoxine-dependent epilepsy and its early management in cases with resistant seizures; even in the presence of extreme prematurity with its neurological consequences.

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Seizures responding to pyridoxine fall into one of 3 categories: Seizures responsive to pyridoxine that necessitate lifelong pyridoxine intake such as "pyridoxine-dependent epilepsy" (PDE), seizures responsive to pyridoxine, but not requiring lifelong pyridoxine, "pyridoxine-responsive seizures," and those requiring high-dose pyridoxine for the treatment of West syndrome.[1] Pyridoxine-dependent epilepsy first recognized in 1954, is a recessively inherited condition.[1] It is often under-diagnosed due to occasional atypical presentation and infrequent use of pyridoxine in intractable seizures in infancy.[2] It is considered a rare disorder with an incidence of 1:400,000 births.[3] The PDE patients have either early-onset with typical presentation within the first few days of life, or later onset, atypical presentation throughout their first 3 years.[4] The PDE may manifest as early as 20 weeks of gestation, and pyridoxine is considered the only treatment of PDE.[5-7] Our objective in presenting this particular case is to highlight a rare case of PDE, the diagnosis of which was delayed due to concealment by prematurity.

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Case Report. A 3-year-old boy was delivered by emergency cesarean section at 25 weeks of gestation because of antepartum hemorrhage, fetal bradycardia, and distress. Apgar scores were 3 and 5 at one and 5 minutes, and birth weight was 682 grams. He was mechanically ventilated for 3.5 months. He had neonatal jaundice that required exchange transfusions on 2 occasions. Following extubation, he required continuous oxygen therapy for another 15 weeks. Trans-cranial ultrasound at 3 weeks of age showed intra-ventricular hemorrhage (IVH) grade IV in the right lateral ventricle and mild bilateral lateral ventricular dilatation. A brain MRI at 4 months of age showed leukomalacia and mild enlargement of both lateral ventricles, which can be attributed to sequelae of his prematurity (**Figure 1**).

He was noted to have occasional right-sided abnormal limbs movement at 4 months of age, which were previously overlooked by his parents. At 9 months of age, he was admitted to the pediatric intensive care unit (PICU) due to status epilepticus that was controlled by phenobarbitone and phenytoin. The EEG showed frequent brief runs of synchronous bi-temporal spike and wave epileptic discharges during wakefulness and sleep. Repeated EEG, one week later, showed mild background asymmetry. The left hemisphere was of lower amplitude and slower frequency in comparison with the right hemisphere. Bilateral sharp wave epileptic activity was seen mainly at the temporo-occipital and parieto-occipital head regions (**Figure 2**). At 10 months of age he was readmitted to the PICU with status epilepticus. Trials with many antiepileptic medications (AEM) including topiramate were not successful in achieving good seizure control. A few days later, IV pyridoxine generated immediate cessation of all EEG epileptic activities. Thereafter, he was continued on oral pyridoxine and topiramate with complete seizure control. After being seizure-free for 18 months, pyridoxine was gradually weaned over 4 months. One month after stopping pyridoxine, he presented with status epilepticus, which was not well controlled by lorazepam, phenobarbital, or phenytoin. However, it was controlled, almost immediately, after restarting pyridoxine. Further investigations showed elevated urine excretion of α-aminoadipic semialdehyde (α-AASA). Subsequently, the open reading frame (ORF) of the 5q31 aldehyde dehydrogenase (ALDH) 7A1 gene was analyzed and the homozygous mutation, c.1195G>C, was identified. The parents were later confirmed to be carriers of the same mutation.

Discussion. The extreme prematurity that was complicated by IVH and hence brain volume loss and dilatation of the lateral ventricles was the main reason for PDE delayed diagnosis in the present case; this has been reported before.[8] Onset beyond the neonatal period and the initial partial response to AEM were other contributing factors in the delayed diagnosis.

The PDE diagnosis was subsequently suspected due to the refractoriness of seizures and their poor response to various AEM in addition to the immediate electro-clinical response to pyridoxine re-administration one

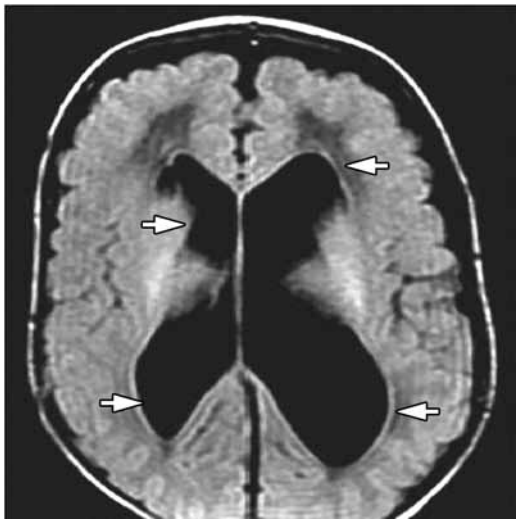

Figure 1 - Brain MRI at 4 months of age showing leukomalacia and mild enlargement of both lateral ventricles, most likely secondary to intraventricular hemorrhage.

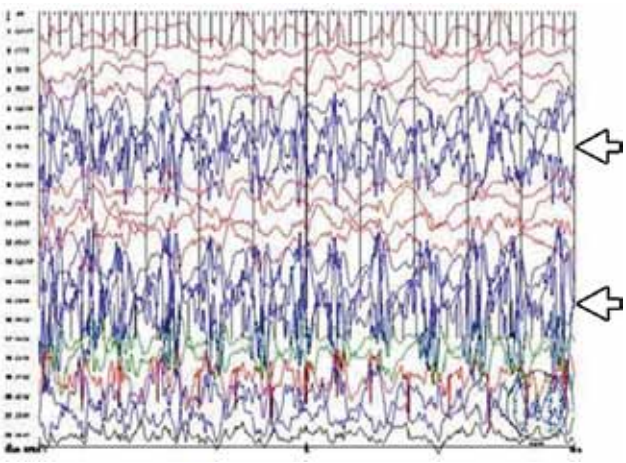

Figure 2 - Patient EEG showed mild background asymmetry. The left hemisphere was of lower amplitude and slower frequency in comparison with the right hemisphere. Bilateral sharp wave epileptic discharges can be appreciated at the temporo-occipital and parieto-occipital areas.

month after its withdrawal. Both, the highly elevated urine excretion of α-AASA, and the pathological mutation identified in the 5q31 ALDH 7A1 gene confirmed the diagnosis.[9]

In conclusion, the early diagnosis of PDE and initiation of the right treatment is important to minimize the potential serious and at times irreversible neurological complications.[10] Prematurity and its neurological complications including seizures should not stand against the likelihood of PDE as a possible diagnosis in cases with malignant seizures not responding to conventional therapy.

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