Management of Status Epilepticus in Pyridoxine Dependent Seizures (PDS)

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A boy was born at term vaginally and had birth weight of 2.35kg with low Apgar scores. At 2 hours of life the child had refractory seizures which were controlled only after intravenous pyridoxine. Electroencephalogram (EEG) done at day 10 of life showed spikes originating from both temporal areas. MRI brain was suggestive of normal myelination. Repeat EEG after 3 weeks was normal. The child was put on phenobarbitone, phenytoin, levetiracetam and 100 mg oral pyridoxine. The child had significant developmental delay. Since the child was seizure free since the neonatal period, to confirm pyridoxine dependency as per the criteria proposed by Baxter et al (1), we decided to stop pyridoxine in this case. Two weeks after stopping pyridoxine, the child was brought in status epilepticus which were not controlled with conventional anticonvulsants and aborted only after administration of 100 mg of IV pyridoxine. No EEG monitoring was done. The child was restarted on 100mg oral pyridoxine. Six months later this child again presented with status epilepticus after an episode of viral fever inspite of regular oral pyridoxine and this time also, responded only after IV pyridoxine was given. Subsequently the maintenance dose of oral pyridoxine was increased to 150 mg per day.

Pyridoxine dependent seizure (PDS) is a rare autosomal recessive disorder, localized to chromosome 2q31. (2) It results from an abnormality of the enzyme glutamic acid decarboxylase (GAD), which results in pyridoxine dependent reduced synthesis of the inhibitory neurotransmitter gamma amino butyric acid (GABA) from glutamate. Mutation in ALDH7A1 is known to cause PDS. (3) Elevated concentrations of pyrocoll acid in plasma and CSF, elevated urinary concentration of α-aminoisadipic semialdehyde (AASA) are shown to be associated with PDS. (3) The clinical features are varied. The full range of symptomatology is unknown. (2) Classically seen in neonatal period but may be seen in later age group too and may be associated with autism, breath holding spells and severe mental retardation. (2) Other reported features include hepatomegaly, bilious vomiting, transient visual agnosia, squint, severe articulatory apraxia, motor dyspraxia and microcephaly. Most common seizure type is generalized tonic clonic seizures that progress to status epilepticus. Other types of seizures reported in the literature include brief partial seizures, tonic and myoclonic seizures and infantile spasms. (4) Criteria for the diagnosis of pyridoxine-dependent epilepsy include (i) seizures resistant to traditional antiepileptic therapy and cessation of clinical seizures with administration of parenteral or oral pyridoxine, (ii) complete seizure control on pyridoxine monotherapy, (iii) recurrence of seizures upon pyridoxine withdrawal; and (iv) no clinical evidence of pyridoxine deficiency. (4) Baxter et al (1) have proposed new criteria. Definite cases have recurrent (two or more) seizures of any type that (i) cease within seven days of the administration of oral pyridoxine (usual dose, 30 mg/kg/day; minimum dose, 15 mg/kg/day; maximum dose 50 mg), (ii) recur when pyridoxine supplementation is withdrawn, and (iii) cease again when pyridoxine is given as above.

The case highlights the fact that pyridoxine dependent seizures can recur within 2 – 23 days of stopping pyridoxine (5) and there can be breakthrough seizures despite maintenance doses of pyridoxine (Vitamin B6) during febrile period. (1) The exact dose of vitamin B6 is still debated. There is a relatively wide range for the daily B6 dose necessary to control the seizure i.e., 10–200 mg/day. In the literature doses as high as 680 mg initially and 200 mg/day subsequently have been reported. (6) Studies show that the dose of vitamin B6 required to normalize the cerebrospinal fluid (CSF) glutamate is 10mg/kg/day than the dose required to control seizures, and the higher dose to achieve normal glutamate level was associated with a normal developmental outcome and improvement in the motor/performance subscale. (7,8)

To conclude, bolus parenteral pyridoxine should be given in all cases of PDS if they present with breakthrough seizures and maintenance dose should be increased. Since measurement of CSF glutamate levels may not be feasible, clinical judgment should be used while deciding on the dose.

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References:

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Letter to Editor (Viewer’s Choice)

Pramila Verma, Neeti Agrawal, Mahesh Maheshwari, Vijaya Beohar

A four years old female child was referred to our hospital with continuous fever and rash over extremities since 15 days. She also had pain in limbs and bilateral pedal swelling since 15 days. She developed multiple painful nodular swelling over both upper and lower limbs on day 5 of fever. Her left ring finger and right 4th toe became black on day 10 of fever. There were no respiratory, cardiac, neurological, renal or gastrointestinal symptoms. The diagnosis of referring pediatrician was septicemia. After admission, she clinically deteriorated. She had fever almost daily and pain in limbs was increasing. She developed palmar erythema and erythematous papules on the dorsum of both feet. Her vitals including blood pressure were normal. Skin examination revealed multiple patchy, maculopapular rash, livido reticularis, subcutaneous tender nodules and evolving gangrene over left ring finger and right 4th toe. Systemic examination was unremarkable. Initial tests revealed hemoglobin of 8.9 g/dl, total leucocyte count of 40,600 cells/cumm with 74% polymorphs, platelet counts of 6,60,000 cells/cumm and erythrocyte sedimentation rate of 24 mm at end of 1 hour. Serum creatine phosphokinase was 22 IU/L, lactate dehydrogenase was 127 IU/L. C-reactive protein and mantoux tests were negative. Urine, serum electrolytes, liver and renal functions tests were normal. Antinuclear antibody (ANA), anticardiolipin antibody (IgG, IgM), ANCA, antistreptolysin O titre, HIV ELISA, Hepatitis B surface antigen and VDRL titres were negative. Blood culture grew coagulase negative staphylococci. Ultrasonography of abdomen and echocardiography were normal. Doppler study of both the lower limbs was normal.

Based on acute onset of gangrene in periphery, livido reticularis, tender subcutaneous nodules, leukocytosis, thrombocytosis, high ESR, negative autoantibodies and raised C-reactive protein, a diagnosis of cutaneous polyarteritis nodosa (c-PAN) was made. Skin histology from lesions showed leukocytoclastic vasculitis with fibrinoid necrosis in the dermal vessels consistent with clinical diagnosis of polyarteritis nodosa (PAN). She was treated with high-dose corticosteroids and cyclophosphamide. Gangrene led to autoamputation of left ring finger whereas toe gangrene which was mild got healed in next few days. She had five relapses in the initial 2 years that were managed by cyclophosphamide and prednisolone. Presently she is on regular follow up and on low dose azathioprine.

Polyarteritis Nodosa (PAN) is a rare autoimmune disease of children. Kussmaul and Maier first described it in 1866. (1) It is characterized by necrotizing vasculitis of small and medium-sized arteries of any organ of the body resulting in ischemia and infarction of affected organ. (2) It can present either in form of cutaneous lesions (c-PAN) or systemic involvement (classic PAN). Classic PAN always presents with involvement of visceral organ (renal, gastro-intestinal system, central nervous system, cardiovascular system)