Establishing an *in vivo* zebrafish platform mimicking seizures in new-born children

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New-born children with neonatal epileptic encephalopathy (NEE) experience violent seizures that usually result in early death or severe mental retardation. NEE is resistant to anti-epileptic drugs, but responds to injections of pyridoxal-5’-phosphate (PLP), one of six forms of vitamin B6. NEE is caused by mutations that inactivate pyridoxine-5’-phosphate oxidase (PNPOx). PNPOx catalyzes the conversion of pyridoxine-5’-phosphate to PLP. PLP is the cofactor for dozens of enzymes, many involved in neurotransmitter synthesis. Rescuing NEE patients with PLP injections results in serious adverse effects, including sensory neuropathy and mental retardation. Improved approaches for developing better therapeutic strategies for NEE are needed. By knocking-down (KD) PNPOx expression in zebrafish, we established and characterized fish that displayed PNPOx mutation-associated epilepsy. Our results showed that morphants expressed: increased spontaneous movement, decreased velocity and acceleration, altered body activity and turning angle. Morphants also showed structural changes: development of dorsalization, abnormal brain and heart structures, shrunken eyes and an unsuccessfully inflated swimbladder. The morphological and behavioral anomalies in the developing larvae were prevented by either co-injecting zebrafish PNPOx mRNA or the addition of PLP in the environment. As with children with NEE the addition of pyridoxine (the substrate for PNPOx) did not relieve symptoms in our zebrafish model. Unexpectedly, pyridoxamine (PM), another form of vitamin B6, also provided rescuing effects. Our data suggested that our PNPOx-KD model may serve as an *in vivo* platform for mutations in PNPOx that cause NEE. The therapeutic potential for NEE treatment by pyridoxamine and our proposed underlying mechanism are described.