

Valproate-induced worsening of seizures in an infant

To the Editor,

Valproate is a strong antiepileptic agent acting as an anticonvulsant drug by increasing the level of gamma aminobutyric acid in the brain (1). Increase in seizures has been rarely reported after use of valproate and it has been attributed to drug intoxication or accompanying metabolic diseases (2,3,4). Here, we want to report a case diagnosed because of increased seizures after use of valproate.

A 6-month-old male patient with resistant seizures was described to have intensive seizures as blinking, licking in the mouth and pulses in the arms. The patient was the fourth child of the parents who had a 1st degree consanguineous marriage and no familial history of similar disease was present. On physical examination body weight was found to be 6500 g (10-25th percentile), height was found to be 67 cm (50-75th percentile) and head circumference was found to be 44 cm (50-75 percentile). The patient was not interested in the surroundings and eye tracking was not present. The pupillae were isochoric and light reflex was positive. Deep tendon reflexes were bilaterally positive in the infant who had not gained control of the head and who was rather hypotonic. Despite phenobarbital, topiramate and oxcarbazepine added to treatment seizures were continuing. Intensive epileptiform discharges were found on electroencephalography which indicated epileptic encephalopathy. On cranial magnetic resonance imaging, delayed myelinization in both brain hemispheres and corpus callosum hypoplasia were observed. Tandem Mass spectroscopy and urine organic acid examination performed to screen congenital metabolic diseases were found to be normal. An increase in the frequency of seizures, period of seizures and tendency to sleep was observed after valproate was added to antiepileptic treatment. Ammonia level was found to be 31 $\mu\text{mol/L}$ (N: 17-55). When the patient's history was interrogated more deeply, it was learned that he had jerks which started in the neonatal period. Nonketotic hyperglycinemia (NKH) was considered in the patient in

whom increase in the frequency of seizures was observed after valproate. Amino acid tests revealed that plasma glycine level was 708 nmol/ml (74-290) and simultaneous glycine level in the cerebrospinal fluid was 148 nmol/ml (3-8). Cerebrospinal fluid/plasma glycine levels ratio was calculated to be 0.20 (a ratio higher than 0.02 is considered to be diagnostic for nonketotic hyperglycinemia).

Nonketotic hyperglycinemia is an autosomal recessive metabolic disease also named as glycine encephalopathy. Defect in the enzyme system which breaks down mitochondrial glycine causes accumulation of glycine in the nervous tissue. The most common neonatal form of the disease is manifested with progressive lethargy, hypotonia, hiccups and seizures in the first days of life. Atypical forms present at older ages and with different clinical pictures. A high ratio of cerebrospinal fluid/plasma glycine supports the diagnosis (5). In animal studies performed with valproate, it was shown that the drug prevented the enzyme system which breaks down mitochondrial glycine and increased glycine levels (6). Valproate related encephalopathy has been reported in patients with ure cyclus defect and carnitine deficiency with a higher rate (3,7). With this case we would like to emphasize that nonketotic hyperglycinemia which also has atypical forms is another metabolic disease which should be considered in cases where the frequency of seizures is increased or the level consciousness is deteriorated after valproate.

Barış Ekici, Erhan Aygün*, Burak Tatlı

Istanbul University Medical Faculty, Department of Pediatrics, Division of Pediatric Neurology, Istanbul, Turkey

**Istanbul University Medical Faculty, Department of Pediatrics, Istanbul, Turkey*

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