

# Administering Valproic acid in epilepsy and speech delay in children



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## ABSTRACT

**Background:** Epilepsy is a recurrent seizure without a trigger. Epilepsy is a chronic disease that is often found in children. Valproic acid is an Anti-Epileptic Drug (AED) often given to children. The effect of valproic acid administration on speech delay has rarely been reported. This case study aims to evaluate the effect of administering valproic acid on epilepsy and speech delay in children.

**Case Description:** A 3-year-old girl was referred to Dr. Soetomo Hospital with epilepsy and speech delay. The patient had recurrent unprovoked seizures since the age of 2 years. She had received valproic acid therapy at the previous hospital and was seizure-free for 5 months before being referred to DSH. The girl can speak in one word but lacks two-word meaningful phrases. There was no perinatal history or previous serious illness. Physical examination was within normal limits. The Denver II examination result was suspect because she failed in speech and language. Her hearing test was normal. Valproic acid was then replaced with phenytoin. In follow-up 7 months after the AED was changed to phenytoin, the patient could string words and speak in sentences. A repeat Denver exam reveals normal speech and language aspects.

**Conclusion:** Giving valproic acid to patients with epilepsy may trigger speech delay in children.

**Keywords:** Speech Disorder, Language Disorder, Anti-Epileptic Drug.

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## INTRODUCTION

Epilepsy is a seizure without a trigger.<sup>1</sup> Epilepsy is a chronic disease often found in children and manifests as a “seizure”.<sup>1</sup> A “seizure” is a paroxysmal change in neurologic function induced by the brain’s excessive, hypersynchronous neuron discharge. The term “epileptic seizure” refers to a seizure induced by aberrant neuronal firing instead of a nonpileptic event, such as a psychogenic seizure. The disorder known as “epilepsy” is characterized by recurring, unprovoked seizures. There are several causes of epilepsy, each reflecting underlying brain dysfunction.<sup>1-3</sup>

Seizures are classified into generalized, focal (formerly known as partial), and epileptic spasms. Focal seizures are caused by neural networks exclusive to one brain hemisphere.<sup>4,5</sup> Bilateral distributed neural networks initiate generalized seizures. A seizure might start focally and then spread. Seizures can begin in either the cortex or the subcortical regions. A clinician can frequently categorize the seizure/epilepsy type using a complete history, EEG data,

and auxiliary information, after which an appropriate diagnostic diagnosis and treatment plan is developed using Anti-Epileptic Drugs (AEDs).<sup>1-5</sup>

Although seizure freedom with monotherapy is desired, less than half of patients attain it with the first treatment.<sup>1-3</sup> When switching AEDs, it is best to do it gradually, allowing enough time for the new drug to reach therapeutic levels before discontinuing the prior treatment.<sup>4</sup> One of the AEDs used in epilepsy is Valproic acid.

Valproic acid is one of AEDs that is often given to children. Valproate comes in various forms, including prolonged release, sprinkles, liquid, and IV. It is 90% protein-bound and is very well absorbed orally. VPA inhibits the cytochrome P450 system, increasing the number of AEDs metabolized by this mechanism.<sup>5,6</sup> It also displaces other highly protein-bound medicines, such as PHT, and can potentially increase their free fraction.<sup>7,8</sup> The effect of valproic acid administration on speech delay has rarely been reported. Based on those mentioned above, this case study aims to evaluate the effect of administering valproic acid on epilepsy

and speech delay in children.

## CASE REPORT

A 3-year-old girl was referred to Dr Soetomo Hospital with epilepsy and speech delay. The patient had recurrent unprovoked seizures since the age of 2 years. Has received valproic acid therapy at the previous hospital and was seizure-free for 5 months before being referred to DSH. The girl can speak in one word, such as “eat” or “drink”, say numbers from one to ten and can point to pictures and body parts. The girl lacks two-word meaningful phrases. There was no perinatal history or previous serious illness. There was no family history of seizures and speech problems. Physical examination was within normal limits. The Denver II examination result was suspect because she failed in speech and language aspects (Figure 1).

Her hearing test was normal. Valproic acid was then replaced with phenytoin. In follow-up 7 months after the AED was changed to phenytoin, the patient could string words and speak in sentences. A

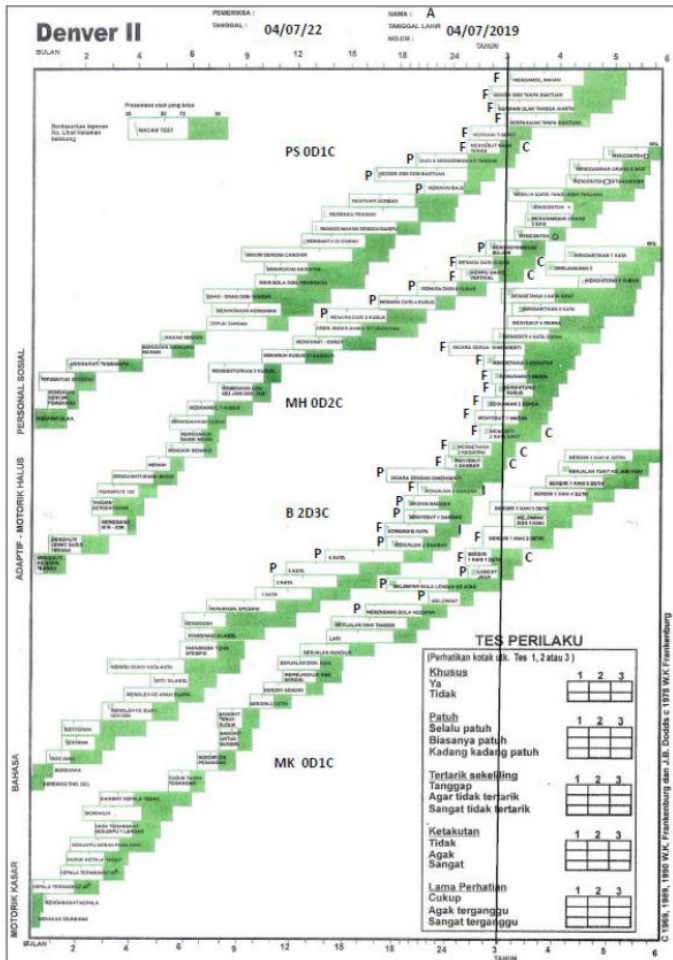


Figure 1. The first Denver II test.

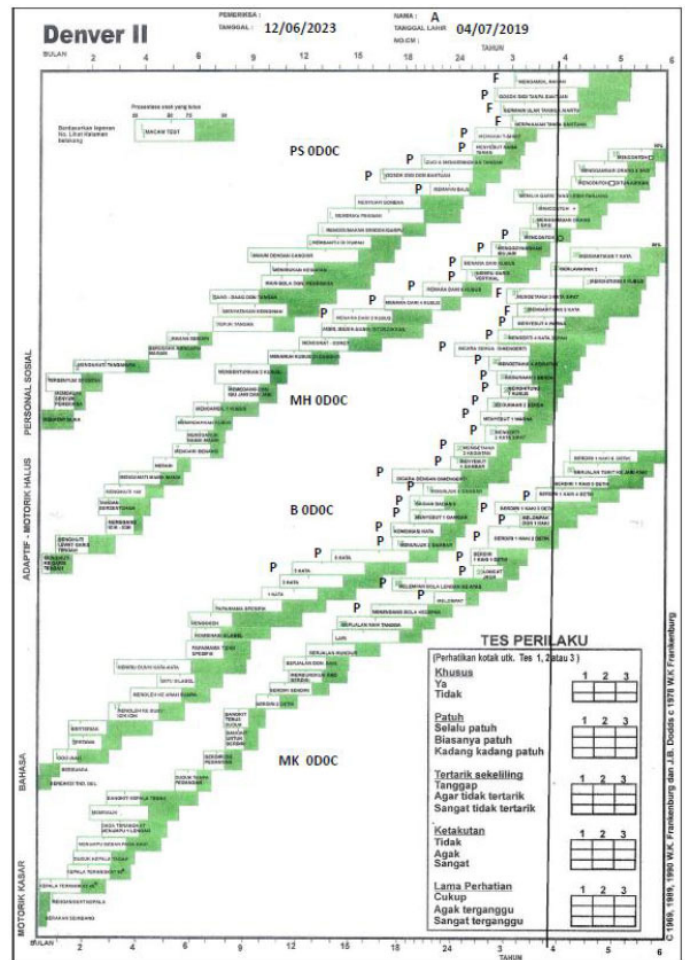


Figure 2. Denver II test 7 months after valproic acid was changed to phenytoin.

repeat Denver exam reveals normal speech and language (Figure 2).

**DISCUSSION**

In this case, a patient with epilepsy had received valproic acid and was seizure-free for 5 months but had a speech delay. Speech improved after AED was changed to phenytoin and after 7 months, speech was normal. Controlling seizures is the most important goal of epilepsy treatment. However, the side effects of AED on cognitive abilities and behavior must be considered when treating children with epilepsy. Speech-language disorders during childhood and adolescence can develop into disorders in learning, reading, and behavior problems and affect the quality of life in adulthood.<sup>1,2</sup>

Valproic acid is one of the most frequently used AEDs in children and is the first-line drug to treat refractory seizures.<sup>1,3</sup> Valproic acid is also available

in liquid preparation, which is easier to administer in children. In a 2013 study in Dr. Soetomo Hospital, were 103 children newly diagnosed with epilepsy. Valproic acid was given to 89.32% of children, with a 75.73% success rate of controlling the seizure.<sup>4</sup>

Valproic acid is one of the first-generation AEDs, along with phenobarbital, phenytoin and carbamazepine. Reported adverse drug reactions (ADR) of valproic acid were less frequent than other first-generation AEDs. However, the impact on cognitive function is still controversial.<sup>1,5</sup> A prospective study by Anderson et al. reported that most ADRs occurred with valproic acid and carbamazepine. The most common ADRs were behavioral problems.<sup>1</sup> A study in Korea reported no significant difference in language functions before and after taking valproic acid therapy.<sup>5</sup> Valproic acid is a histone deacetylases (HDAC)

inhibitor that plays an important role in neurodegenerative diseases such as ASD.<sup>6,7</sup> The effect of valproic acid administration on speech delay has rarely been reported.

Speech and language are one of the areas of child development. Preschool age (2-5 years) is when speech development occurs most rapidly. Vocabulary increases from 50-100 words to more than 2,000 and children begin to combine words.<sup>8</sup> Practically, 90% of children use 2-word sentences by age 2, 3-word sentences by 3 years, and 4-word sentences by 4 years. Sentences become increasingly complex as a child's understanding of language develops. By ages 3 to 4, children can understand and use prepositions (for example, "under" and "above"), adjectives, and adverbs. They started asking and answering questions. Children's pragmatic language skills also develop when children learn the rules of using language in social communication. The red flag of speech

delay at the age of 3 years is a lack of two-word meaningful phrases.<sup>9,10</sup>

History of seizures is a risk factor for children with speech delay compared to normal children.<sup>11,12</sup> In children with a history of seizures, there is hypoxia in the brain, which can cause brain injury and manifest as speech and language delays. Functional magnetic resonance imaging (fMRI) studies show that epilepsy of various underlying etiologies can predispose to language tissue consolidation. In children with benign epilepsy with centrotemporal spikes (BECTS), fMRI demonstrated failure to lateralize normal cortical function. These children had greater bilateral activation for language tasks that usually involve the left hemisphere, including verb construction, sentence construction, and semantic assignment, as well as right hemisphere tasks, such as using different intonations. Similarly, in children with focal epilepsy, fMRI found these patients significantly more likely to demonstrate bilateral activation or right hemisphere language predominance compared to left hemisphere language in control subjects.<sup>2</sup>

Prenatal exposure to valproic acid increases the risk of cognitive disabilities and ASD. The use of valproic acid in pregnant women with epilepsy increases the risk of developmental problems and ASD in the unborn child.<sup>7,13</sup> In vitro studies found that valproic acid causes neurodevelopmental defects primarily by inhibiting the HDAC class I. Research on rats that received valproic acid injection during pregnancy found that valproic acid impairs histone acetylation ALDH1A1 and downregulates the RA-RARA pathway. Epigenetic modifications such as ALDH1A1 by valproic acid lead to synaptic deficits and autism-like behavior.<sup>6,14-17</sup>

The limitation in this report is the causality of speech delay cannot be confirmed due to the effect of valproic acid therapy or other factors. Further case studies are needed to confirm this finding.

## CONCLUSION

Giving valproic acid to patients with epilepsy may trigger speech delay in children.

## CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

## ETHICAL CONSIDERATION

Informed consent was obtained from the patient's family regarding publishing the current report with confidentiality regarding personal information.

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## AUTHOR CONTRIBUTIONS

All authors had contributed to manuscript writing and editing until interpreting the outcome through a case study.

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