

SODIUM VALPROATE: CULPRIT OR SAVIOUR OF ATTENTION DEFICIT HYPERACTIVITY DISORDER?

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SUMMARY

The Pathogenesis of Attention Deficit Hyperactivity Disorder (ADHD) remains controversial. An interplay between neurochemical, neurophysiological & psychosocial factors on a genetically predisposed person seems a possible mechanism. Sodium valproate, a drug that is widely used in the treatment of many psychiatric disorders, has been shown to cause and aggravate hyperactivity in children. This phenomenon has been underreported and underemphasized. We present a case report on a patient who developed ADHD after sodium valproate treatment for his epilepsy and , through a ten -year Medline search & literature review, we discuss possible mechanism of sodium valproate-induced hyperkinesia and its importance in understanding the neurochemical mechanism & hence the treatment of ADHD.

Key Words: attention deficit hyperactivity disorder; sodium valproate; hyperkinesia; sodium valproate-induced hyperkinesia.

INTRODUCTION

The pathogenesis of Attention Deficit Hyperactivity Disorder (ADHD) remains controversial. An interplay between neurochemical, neurophysiological and psychosocial factors on a genetically predisposed person seems a possible mechanism (Sandberg 1996). Neurochemical studies of ADHD have largely been carried out around the catecholamine hypothesis. The role of dopamine, serotonin and norepinephrine have all been implicated but recent studies have shown conflicting results. Neurophysiological factors also play a role in the pathogenesis of ADHD as evidenced by the non-specific abnormal electroencephalogram patterns found in the children with ADHD. Theory like inadequate inhibitory effect from the frontal lobe on the lower parts of the brain leading to disinhibition has also been proposed. From the psychosocial perspective, factors like unhappy family atmosphere (Taylor et al 1991), prolonged emotional deprivation, negative affective content of the primary caregiver-child interaction (Olson et al 1990), overall social disadvantage and absence of rewarding experience are all said to be important in the pathogenesis of ADHD. The theory of minimal brain damage (Strauss & Lehtinen 1947) has gone out of favour. Food additives, colourings and sugar have also been suggested to be possible causes but so far there is still no convincing scientific evidence.

Medications like phenobarbital are also well-known to cause hyperactivity (Hardman et al 1996). However, there have been no systematic studies on the interrelationship between medications and ADHD in recent literature. The relationship between the use of sodium valproate and ADHD has so far received relatively less attention when compared to that of phenobarbital. Nowadays, sodium valproate is widely used in the treatment of psychiatric disorders such as bipolar I disorder, schizoaffective disorder, panic disorder & post-traumatic stress disorder (Kaplan

et al 1996). We believe that it is important for us to report on a patient who developed ADHD after sodium valproate treatment for his epilepsy and we discuss the putative mechanisms.

CASE REPORT

'A' is a 7 year-old boy and the only child of the family. He was born in Hong Kong after a normal pregnancy and delivery. His developmental milestones were delayed. He could only speak complete sentence at the age of 3 and could sit upright on his own at 1 1/2 years old. IQ assessment was done at the age of 6 using WISC-HK and the score was 60. He lived with his parents and his sister in a public housing unit. His paternal grandfather had a history of epilepsy well-controlled with anti-convulsants. Otherwise, there was no other family history of psychiatric illnesses. There were no symptoms of inattention or hyperactivity noted by his parents apart from the delay in developmental milestones.

'A' developed atonic seizures since 1 1/2 years old, presented as attacks in which there was loss of muscle tone followed by dizziness, loss of consciousness and falling to the floor. Each attack lasted from 30 seconds to 1 minute and he came round spontaneously. There were no tongue-biting, uprolling of eyeballs, urinary incontinence or twitching of limbs observed. However, his parents neglected the symptoms until 'A' was 5 years old when they consulted a pediatrician and a diagnosis of atonic seizure was made. Electroencephalogram showed unremarkable findings. Sodium valproate (200mg bd) was prescribed. About one month later, 'A' was noted to have developed some hyperactivity and inattention symptoms such as not being able to sustain a task or play activities, making careless mistakes in school work, being forgetful and easily distractible, losing stationery easily, squirming and then standing up from seat and running about excessively under inappropriate situations. The pediatrician was consulted again. Sodium valproate was stopped and his symptoms of hyperactivity and inattention subsided. However, he started to have dizzy spells and attacks of atonic seizure. He was put back on sodium valproate. The seizure was under control but symptoms of hyperactivity and inattention again resumed. 'A' was finally referred to

a child psychiatrist for assessment. The level of sodium valproate was within therapeutic range.

During the interview, 'A' appeared restless and could hardly sit still on his chair. He fidgeted with his fingers and tried to reach out for things on the table frequently. He appeared euthymic. His speech was coherent and relevant and there were no psychotic features noted. 'A' was diagnosed to have Attention Deficit Hyperactivity Disorder (ADHD) and he was prescribed methylphenidate 5 mg o.m. He became significantly calmer, less hyperactive and more attentive after taking the medication.

DISCUSSION

This case illustrates a possible aetiological relationship between the use of sodium valproate and ADHD. To our knowledge, this case report is the only one reported in recent English medical literature on this theme.

Among the commonly used anticonvulsants, phenobarbital is notorious for causing irritability and hyperactivity in children although the exact mechanism is still not known (Hardman et al 1996). Sodium valproate is another anticonvulsant which has been noted to cause hyperactivity and behavioural disturbance (Chadwick et al 1989, Davis et al 1994). Its anticonvulsant properties were discovered serendipitously (Hardman et al 1996). The exact mechanism of its anticonvulsant properties is still unknown but is thought to involve enhancement of GABA-mediated inhibition, limitation of sustained repetitive firing of neurones, reduction of effects of excitatory neurotransmitters (Walton et al 1993) and alteration in monoamine levels in the brain (Baf et al 1994).

A case of a 8 year-old girl who manifested dramatic behavioural and intellectual disorder after she had been treated with valproate has been reported. (Vaquerizo et al 1995). In fact, hyperkinesia associated with use of sodium valproate has been well-documented in recent studies (Davis et al 1994). Some authorities consider that sodium valproate has a greater than expected effect on psychomotor function (Gallassi et al 1992).

Possible mechanism of valproate-induced hyperkinesia involves alteration in the level of monoamines in the brain. Valproate is known to increase the level of norepinephrine in the hypothalamus, the level of dopamine in motor cortex, hippocampus and hypothalamus, also the serotonin level in the striatum-accumbens and the brain stem in the rat brain (Baf et al 1994). In fact, the alteration in monoamine levels in the brain is said to account for its anticonvulsant properties (Baf et al 1994).

The exact neurochemical mechanism for sodium valproate to cause ADHD appears complicated. Serotonin level in the brain was said to correlate significantly with hyperactivity and impulsivity (Castellanos et al 1995) which might be the reason why sodium valproate can cause hyperactivity. However, studies of serotonin level have been inconsistent. There is also a conflicting study which showed that sodium valproate and methylphenidate might actually have similar effect on the arousal processes in ADHD (Frank 1993) and hence might be useful in treating ADHD. Another hypothesis is the norepinephrine hypothesis which states that norepinephrine depletion causes hyperactivity in ADHD. The beneficial effect of the new SNRI

venlafaxine on the treatment of ADHD is also said to arise from the inhibition of norepinephrine reuptake (Pleak et al 1995). If this is so, then it would be very difficult to understand why sodium valproate, which increases the norepinephrine level in the brain, can cause hyperactivity. All these point against the proposal that the mechanism of valproate-induced hyperkinesia acts via alteration of the level of a single monoamine in the brain. This actual neurochemical model therefore seems to be a more complicated one — probably an interplay between several monoamines, different receptor subtypes and possibly other transmitters as well. Further researches can be done on this aspect but unfortunately, there are a large array of etiological factors which can result in the appearance of ADHD, aggravate ADHD, caused by ADHD, or share common causal features. These all contribute to the complexity of the clinical "syndrome" of ADHD and difficulties in defining its boundaries (Hales et al 1994). Nevertheless, it is interesting that sodium valproate can induce hyperkinesia on the one hand but can improve hyperkinesia on the other. To look for the factors that determine which pharmacodynamic effect sodium valproate has on ADHD remains a challenge to all child psychiatrists.

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