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Valproic Acid Therapy Causes Subclinical Hypothyroidism in Children with Epilepsy

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Kim SH, Chung HR, Kim SH, Kim H, Lim BC, Chae JH, Kim KJ, Hwang YS, Hwang H. Subclinical hypothyroidism during valproic acid therapy in children and adolescents with epilepsy. Neuropediatrics 2012;43:135-9. Epub May 22, 2012; doi: 10.1055/s-0032-1313913.

SUMMARY

Background

Anticonvulsants have been responsible for alterations of thyroid function in several ways. In patients with hypothyroidism who are undergoing levothyroxine therapy, phenobarbital and carbamazepine can accelerate the degradation and increase the dose requirement for L-T_4. Diphenylhydantoin may interfere with thyroxine binding to binding proteins and thereby reduce T_4 levels. The current report is a study of the effect of valproic acid on thyroid function in children with epilepsy.

Methods

The investigators studied 61 ambulatory children with epilepsy who had taken valproic acid (VPA) for more than 6 months, who had normal school function, normal MRI images, good seizure control, and absence of systemic disorders. For controls, they studied 144 age- and sex-matched children who visited the outpatient clinic during the same period at the Pediatric Department of Seoul University. Patients and controls each had thyroid-function tests and had follow-up tests on the same dose of valproic acid if an abnormality was found. Patients with abnormal tests were referred to a pediatric neurologist. Thyroid tests included measurement of TSH, FT_4, total T_3, and anti-TPO. Serum valproic acid was also measured.

Results

The mean age of the children was 10 years. The mean TSH in the VPA group was higher than that in the control group (4.6 vs 2.7 mU/L, $P<0.01$); FT_4 was slightly higher and T_3 slightly lower in the VPA group as compared with the controls. None of the children had positive anti-TPO. TSH >4 mU/L was found in 52% of the VPA group as compared with 17% of controls ($P<0.001$); TSH >10 mU/L was found in 8.2% of the VPA group as compared with none of the controls ($P<0.001$). No clinical features of hypothyroidism were found in the evaluation by the endocrinologist.

On follow-up, 61.5% (16 of 26) of patients exhibited a persistently elevated TSH level. When eight patients with subclinical hypothyroidism underwent follow-up thyroid-function tests 3 months after discontinuing VPA therapy, seven showed a decrease in TSH level to the normal range. The serum valproate level was significantly higher in the 32 children with subclinical hypothyroidism than in the 29 with normal TSH (97.4±35.8 vs. 70.6±29.4 µg/ml, $P<0.005$) and the VPA dose was greater (25±6 mg vs. 20±5 mg/kg/day, $P<0.001$).

Conclusions

Subclinical hypothyroidism is prevalent among children with epilepsy on VPA therapy. This seems to justify screening for thyroid dysfunction during VPA therapy, especially when a high dose of VPA is used.

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ANALYSIS AND COMMENTARY

The 50% frequency of slightly elevated serum TSH in patients taking valproic acid is higher than the 26% reported this year in a study of 57 Indian children taking this anticonvulsant (1). More importantly, subclinical hypothyroidism, with TSH >10 mU/L, occurred in 8.2% of patients in the current study, but no treatment for subclinical hypothyroidism was recommended. If one were to apply conservative recommendations for adults with this degree of subclinical hypothyroidism, the children would have been treated with levothyroxine (2).

Although valproic acid has been used for the treatment of epilepsy for over 40 years, its mechanism of action is still unclear; this is also the situation with regard to the basis for the elevation of serum TSH. Valproic acid could increase serum TSH by affecting the complex central neuroendocrine control of TSH release that in turn might elevate serum FT_4. Unfortunately, the serum FT_4 was not reported in the patients with either degree of elevated serum TSH. However, if the TSH elevation persisted with higher FT_4, there would be suppression feedback to reduce the serum TSH level. Valproic acid also inhibits histone deacetylase, so it can modify transcription of many genes. The pathophysiology of the TSH elevation requires further investigation, as does the treatment of the subclinical hypothyroidism in these children.

References

1. Sahu JK, Gulati S, Kabra M, Arya R, Sharma R, Gupta N, Kaleekal T, Reeta KH, Gupta YK. Evaluation of subclinical hypothyroidism in ambulatory children with controlled epilepsy on valproate monotherapy. J Child Neurol 2012;27:594-7. Epub November 22, 2011.
2. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA. 2004; 291:228-38.