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Seizure during Graves' disease

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ABSTRACT – Occurrence of seizure during Graves' disease is very rare. According to Lin *et al.* (1992), only 13 cases were published between 1956 and 1992. Since then, four other cases have been published, resulting in a total of 17 papers in 40 years (Li *et al.* 2000, Lee *et al.* 1997, Radetti *et al.* 1993). We report, in this paper, the case of a young girl treated for recurrent Graves' disease who presented a generalized seizure.

Key words: seizure, thyrotoxicosis, Graves' disease, generalized seizure

Observation

An 18-year-old girl with no history of medical problems, except for an allergy to acarus, presented a first episode of Graves' disease. She was successfully treated for 18 months with carbimazole and levothyroxine. Thyrotropin (TSH) was measured as 2.31 µUI/L (normal (N) = 0.18-4 µUI/L), serum-free thyroxine (FT4) as 14.7 pmol/L (N = 11.7-26 pmol/L), and thyroid stimulating immunoglobulin (TSI) was negative after treatment interruption. Two years later, she had a recurrence of hyperthyroidism; TSH < 0.05 mUI/L, FT4 > 70 pmol/L, free triiodothyronine (FT3) = 38.3 pmol/L (N = 4-8 pmol/L) and TSI = 35 U/L (N < 9 U/L), and was also treated with anti-thyroid drug (40 mg of carbimazole and 50 µg of levothyroxine). After two months of treatment, she was in a euthyroid state (FT4 = 17 pmol/L, FT3 = 4.9 pmol/L). Because of neutropenia (3 000 white cells/mm^3, 34% neutrophils and 56% lymphocytes), the anti-thyroid drug was changed to 300 mg of propylthyouracile (PTU) and 50 µg of levothyroxine. Ten days later, the patient stopped treatment for 24 hours and presented a generalized seizure which was considered as a first episode by the neurologist. This occurred in the morning, after her bath without prodroma. Family members were alerted by the noise of her fall. She was unconscious, with arm and leg clonns, fast breath and remained confused for about 20 minutes after the episode. No urine loss was noted but she bit her tongue on the left side. After the episode, the patient had complete amnesia. No triggering factor was identified. She had headaches the day after the episode when the neurologist examined her. An EEG was performed after treatment with clobazam which showed a basic rhythm of 7-8 hertz, overloaded with treatment-related fast activities. Strong hyperpnea showed some evidence of bilateral and symmetric slow waves, with few spike aspects. Stimulation Light Intermittent (SLI) was ineffective. Further hyperpnea reproduced the same result and EEG was within normal limits. Etiologic assessments were all negative (biological parameters, EEG and scan). She responded well to anti-thyroid treatment with normal FT4/FT3 values measured 8 days later (FT4 = 12.5 pmol/L, FT3 = 5.9 pmol/L). Recurrence of neutropenia with PTU (GB = 8 800, 5 300, 2 600 white cells/mm^3 on weekly counts) led us to perform a subtotal

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thyroidectomy. Twenty-four hours after surgical treatment, the patient presented a second generalized seizure. This post-operative episode occurred again in the morning, with loss of consciousness and clonisms. EEG was performed several hours later and again showed diffuse paroxystic abnormalities. Neurological examination was otherwise normal. Again, there was no evidence of a triggering factor, such as sleep deprivation, alcohol consumption or light stimulation. Anti-epileptic treatment was initiated for 6 months. The thyroid biochemical parameters remained normal (TSH = 2.16 mUI/L, FT4 = 12.4 pmol/L, FT3 = 2.3 pmol/L) and TSI was positive (22 U/L) and no seizures occurred in the following months.

Discussion

The association of seizure and Graves' disease is rare. According to the literature, generalized seizures have been described for untreated hyperthyroidism (Lin *et al*. 1992, Lee *et al*. 1997, Primavera *et al*. 1990) or recurrence of thyrotoxicosis (Li *et al*. 2000, Korczyn and Bechar 1976). Seizures can also occur during acute thyrotoxic crisis, resulting from intercurrent pathologies such as infection, surgical treatment or stress (Roth and McAuliffe 1989). The underlying physiopathology is not clearly understood. Thyrotoxic seizures result mainly from the direct effect of thyroid hormones on brain cells (Jabbari and Huott 1980). Cerebral blood flow and oxygen consumption in hyperthyroidism are not significantly increased (Sokoloff 1953). EEG can show abnormalities but alpha rhythm increase is not explained by hyperthermia (Leubuscher *et al*. 1988). Our patient had moderate thyrotoxicosis that was corrected by treatment and EEG was normal. Moreover, generalized seizure recurrence occurs under treatment with an euthyroid state, which has been already reported in the literature. Indeed, Ahmad and Cohen (1981) described thyroid storm with a normal serum triiodothyroid level in a diabetic patient with ketoacidosis. There are several hypotheses that explain the occurrence of generalized seizures in the euthyroid state. Firstly, the interruption of treatment over several days may have an effect. This is improbable in our case since biochemical thyroid parameters were within the normal range 15 days before and 8 days after the seizure. The treatment was taken regularly with good compliance. Secondly, anti-thyroid drug malabsorption may influence the occurrence of seizures. Our patient did not describe any gastrointestinal disorders in the days preceding hospitalisation. There was no vomiting, dysentery or possible drug interaction with other oral treatment. Thirdly, PTU neurological toxicity can also be a contributing factor. To our knowledge, there is no report that supports this hypothesis. PTU has one to two hours of plasmatic half-life, with strong protein binding and an active action of 12 to 24 hours (Hoffman and Miceli 1988). Hence, one-day treatment interruption will not induce thyroid hormone increase. Finally, it is possible that the patient has an epileptic syndrome of some kind as well as Graves' disease; seizure recurrence might thus be merely "coincidence".

Conclusion

Our case report suggests that generalized seizures can occur, not only in the thyrotoxic state, but also within normal thyroid biochemical parameters; only follow-up will allow us to differentiate between a genuine epileptic syndrome and a possible association with Graves' disease; EEG may also sometimes aid interpretation of the etiology. Although it may be diffficult to differentiate between hyperthyroidism and cryptogenetic epilepsy, the data reported here favor thyrotoxicosis as a cause of seizure. □

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