NOTE

An Infant Case of Graves' Disease with Ophthalmopathy

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Abstract. Graves' disease is a rare disorder in children, particularly in infants. Ocular manifestations of Graves' disease in children are even more rare and are mild compared to adults. We report a 3-year-old girl with Graves' ophthalmopathy who visited our clinic because of lacrimation. Her family had also noticed exophthalmos, goiter, irritability and increased appetite for more than 3 months. The ophthalmologist noted bilateral proptosis, eyelid erythema, lacrimation, entropion of the lower eyelid, and superficial keratitis. Her serum concentrations of free thyroxine and free triiodothyronine were high, and thyroid-stimulating hormone (TSH) was low. Serum samples were markedly positive for antibodies to TSH receptor (TRAb) and thyroid-stimulating antibody (TSAb). Although hyperthyroidism was controlled with propylthiouracil within 3 weeks, her eye signs did not improve. We administered methylprednisolone pulse therapy for ophthalmopathy, but the effect was limited and the lacrimation due to entropion and superficial keratitis persisted. Titers of both TRAb and TSAb decreased slightly and transiently with the pulse therapy. One year later, both titers remained high and eye signs did not improve any more though she was clinically euthyroid. This might indicate that both TRAb and TSAb levels correlate with the clinical course. Therefore, TRAb or TSAb might be good indicators of progress of Graves' ophthalmopathy. Ocular manifestations of Graves' disease should be followed closely with measurements of both TRAb and TSAb even in infant cases.

Key words: Graves' ophthalmopathy, Infant, Methylprednisolone pulse therapy

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OCULAR symptoms are the major and usually specific manifestations of Graves' disease [1, 2]. There are two types of ocular symptoms, namely, thyrotoxic manifestations and infiltrative ophthalmopathy. Thyrotoxic manifestations (including lid lag and stare) develop secondary to the hyperactivity of sympathetic nerves, and abate when the thyrotoxicosis is relieved. Infiltrative ophthalmopathy, on the other hand, may follow an independent course from the thyrotoxic manifestations and is often not influenced by treatment with thyroid blockers. Infiltrative ophthalmopathy is

evident in more than 50% of patients, but is much less common in children than in adults [3]. Moreover, the severity of ocular involvement is definitely less than in adults [3–5]. Graves' disease is reported to be rare before the age of 10 years, and very rare before 5 years of age [1]. Therefore, the information on Graves' ophthalmopathy is less well established in children than in adults.

In this report, we describe an infant case with Graves' ophthalmopathy in whom methylprednisolone pulse therapy was adopted.

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Case Report

A 3-year-old girl visited Okayama Medical Center because of lacrimation in March 2004. Between De-

ember 2003 and February 2004, no pediatricians or ophthalmologists at other clinics detected any organic abnormalities though her family complained of her lacrimation. However, family members also noticed exophthalmos, goiter, irritability and increased appetite.

At our clinic, physical examination revealed height was 99.0 cm (+1.20 SD), weight was 15.5 kg (+1.12 SD), and percent overweight was 2.6% [6]; blood pressure was 134/50 mmHg, and pulse rate, 140 beats/min with regular rhythm. Bilateral proptosis, eyelid erythema, lacrimation, entropion of the lower eyelid and superficial keratitis were observed (Fig. 1a). There was no Graefe's sign or marked lid retraction; proptosis could not be evaluated due to lack of patient cooperation. The enlarged thyroid gland was diffuse, had a soft texture by palpation, and nodules were not detected. A bruit was heard at the goiter, but no abnormalities of the chest or abdomen were found.

Laboratory studies revealed high serum levels of alkaline phosphatase, at 1,310 IU/L (normal range, 290 to 1,000 IU/L), and creatine kinase, at 222 IU/L (normal range, 45 to 163 IU/L). No other abnormalities of blood analysis or urinalysis values were noted. Evaluation of thyroid function showed the following values: free thyroxine (FT₄) was 4.81 ng/dL (normal range, 0.70 to 1.48 ng/dL), free triiodothyronine (FT₃) was 22.1 pg/mL (normal range, 1.71 to 3.71 pg/mL), TSH was less than 0.01 mIU/L (normal range, 0.35 to 4.94 mIU/mL). Titers of anti-thyroglobulin antibodies (TgAb) and thyroperoxidase antibodies (TPOAb) were 14,545.4 IU/mL (normal range, 14.1 to 40.6 IU/mL) and 856.1 IU/mL (normal range, 1.1 to 5.2 IU/mL), respectively. TSH receptor antibody (TRAb) level measured by a commercial radioreceptor assay (TRAb Cosmic III, Cosmic Corp., Tokyo, Japan), was 70.2% (normal range, less than 15%) and thyroid-stimulating antibodies (TSAb), measured by a radioimmunoassay using porcine thyroid cells (TSAb Kit Yamasa, Yamasa Corporation, Choshi, Japan), was 3,287% (normal range, less than 180%). There was no evident swelling of the extraocular muscle by magnetic resonance imaging (MRI).

Clinical thyrotoxicosis and eye changes established a diagnosis of Graves' disease with ophthalmopathy. Eye changes were class 2-0 according to the American Thyroid Association system that uses the mnemonic NOSPECS [7] because of lacrimation and inverted eyelashes.

Treatment with propylthiouracil 5 mg/kg/day every

8 hours was started. Within 3 weeks, thyroid function returned to normal, but the eye symptoms showed no improvement. Therefore, methylprednisolone pulse therapy (30 mg/kg for three days) was started. Although the eyelid erythema disappeared, the other eye signs did not show further improvement (Fig. 1b). As shown in Fig. 2, the titers of both TRAb and TSAb decreased transiently, but then increased again. One year later, in May 2005, she was clinically euthyroid, but her eye changes were still class 2-0. Both TRAb and TSAb levels remained high at 82.3% and 3,667%, respectively.

Fig. 1. Photograph of both eyes: (A) before therapy (B) 2 weeks after pulse therapy

Fig. 2. Changes in TRAb and TSAb after initiation of treatment of propylthiouracil. mPSL: methylprednisolone pulse therapy.

Discussion

Published literature indicates that infiltrative ophthalmopathy is very rare in children and adolescents and severity is less than in adults [3, 5, 8]. Chan *et al.* recently compared the clinical presentation in Chinese patients with previously reported studies, which were mainly in Caucasians [4]. The Chinese patients showed the highest proportion with positive ocular manifestations, but no cases had debilitating myopathy or complications that threatened the vision. Wada *et al.* reported 4 Japanese infant cases with Graves' ophthalmopathy, with entropion in 3 cases; no swelling of the medial rectus muscle was demonstrated by MRI [9]. Incidence of Graves' disease in adults in England was reported to be 15–20 per 100,000 per year [10], however, was reported to be rare, and the calculated incidence was only 0.79 per 100,000 in Danish children [11]. On the other hand, a recent study in Hong Kong Chinese documented an incidence of 6.5 per 100,000 children [12]. Furthermore, the incidence of exophthalmos itself in children with Graves' disease in Japan and that in the West have little difference (60–70%) [13]. These documents might indicate that Oriental children tend to develop Graves' ophthalmopathy more frequently than Caucasians. Further studies are required to reveal possible genetic or environmental factors for such epidemiology.

Although our patient complained of lacrimation due to entropion, the condition is rare in adults with Graves' ophthalmopathy [14]. Also, entropion was not described in children in other studies, except that of Wada *et al.* Entropion is not due to thyrotoxicosis but to secondary anatomical abnormalities. Epiblepharon commonly occurs in Japanese infants; 4449 Japanese children were examined for epiblepharon associated with inverted eyelashes and 441 cases of this condition were observed [15]. Therefore, Japanese infants with Graves' disease, including our case, might show a tendency to have entropion due to

epiblepharon as well as lower lid retraction.

Since ocular involvement in Graves' disease in children is less frequent and much less severe than in adults, most patients only require treatment with lubricating eye drops. In the present case, the eye signs did not improve in spite of euthyroid state and there was concern about worsening superficial keratitis; consequently, methylprednisolone pulse therapy was administered. Now glucocorticoid therapy is recommended for patients with severe or active ophthalmopathy in children as well as in adults [1, 7, 16]. Morocco *et al.* reported that pulse therapy resulted in a favorable clinical response in 88% of patients, as compared with a response rate of 63% in patients given oral glucocorticoid therapy, and that there were fewer side effects in the pulse therapy group than in the oral therapy group [17]. We adopted pulse therapy because erythema of the eyelids implied active ophthalmopathy [7] and a lower risk of side effects was expected. The dose was tolerated, but not fully effective.

Though the pathogenesis of infiltrative ophthalmopathy is still unresolved, it has been suggested that autoantibodies to an antigen cross-reacting with the TSH receptor may be involved [18]. Watanabe *et al.* reported the relationship between TSAb activity and severity of ophthalmopathy [19]. In our case, the titers of both TSAb and TRAb decreased slightly and transiently during methylprednisolone therapy; these changes correlated with ocular manifestations. As epiblepharon tends to disappear spontaneously with age one should not neglect the possibility that entropion will spontaneously improve with age too. However, one should consider other conservative medical managements (*e.g.*, γ -globulin, octreotide) or surgical approaches immediately when there is concern of worsening of superficial keratitis.

In conclusion, ocular manifestations should be followed closely even in infant cases, and particularly in Orientals, with Graves' disease.

References

1. Larsen PR, Davies TF, Hay ID (1998) The thyroid gland. In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR (eds) *Williams Textbook of Endocrinology*, 9th ed. WB Saunders, Philadelphia, 430–451.
2. Fisher DA (1989) The thyroid gland. In: Brook CGD, Grumbach MM (eds) *Clinical Paediatric Endocrinology*. Blackwell Scientific Publications, Oxford, 326–329.
3. Grüters A (1999) Ocular manifestations in children and adolescents with thyrotoxicosis. *Exp Clin Endocrinol Diabetes* 107 (Suppl 5): S172–S174.
4. Chan W, Wong GWK, Fan DSP, Cheng ACK, Lam DSC, Ng JSK (2002) Ophthalmopathy in childhood

- Graves' disease. *Br J Ophthalmol* 86: 740–742.
5. Uretsky SH, Kennerdell JS, Gutai JP (1980) Graves' ophthalmopathy in childhood and adolescence. *Arch Ophthalmol* 98: 1963–1964.
 6. Asayama K, Ozeki T, Sugihara S, Ito K, Okada T, Tamai H, Takaya R, Hanaki K, Murata M (2003) Criteria for medical intervention in obese children: A new definition of obesity disease in Japanese children. *Pediatr Int* 45: 642–646.
 7. Perros P, Dickinson AJ (2004) Ophthalmopathy. In: Braverman LE, Utiger RD (eds) *Werner & Ingbar's The Thyroid*, 9th ed. JB Lippincott, Philadelphia, 474–487.
 8. Young LA (1979) Dysthyroid ophthalmopathy in children. *J Pediatr Ophthalmol Strabismus* 16: 105–107.
 9. Wada S, Ohno T (1999) Thyroid ophthalmopathy in children. *Ganka Rinsho Iho* 93: 600–602 (In Japanese).
 10. Barker DJ, Phillips DI (1984) Current incidence of thyrotoxicosis and past prevalence of goiter in 12 British towns. *Lancet* 2: 567–570.
 11. Perrild H, Lavard L, Brock-Jacobsen B (1997) Clinical aspects and treatment of juvenile Graves' disease. *Exp Clin Endocrinol Diabetes* 105 (Suppl 4): S55–S57.
 12. Wong GW, Cheng PS (2001) Increasing incidence of childhood Graves' disease in Hong Kong: a follow-up study. *Clin Endocrinol* 54: 547–550.
 13. Segni M, Leonardi E, Mazzoncin B, Pucarelli I, Pasquino AM (1999) Special features of Graves' disease in early childhood. *Thyroid* 9: 871–877.
 14. Bartley GB, Fatourehchi V, Kadrmas EF, Jacobsen SJ, Ilstrup DM, Gamity JA (1996) Clinical features of Graves' ophthalmopathy in an incident cohort. *Am J Ophthalmol* 121: 284–290.
 15. Noda S, Hayasaka S, Setogawa T (1989) Epiblepharon with inverted eyelashes in Japanese children. I. Incidence and symptoms. *Br J Ophthalmol* 73: 126–127.
 16. DiGeorge AM, LaFranchi S (1996) Hyperthyroidism. In: Behrman RE, Kliegman RM, Arvin AM (eds) *Nelson Textbook of Pediatrics*, 15th ed. WB Saunders, Philadelphia, 1600–1601.
 17. Marcocci C, Bartalena L, Tanda ML, Manetti L, Dell'Unto E, Rocchi R, Barbesino G, Mazzi B, Bartolomei MP, Lepri P, Cartei F, Nardi M, Pinchera A (2001) Comparison of the effectiveness and tolerability of intravenous or oral glucocorticoids associated with orbital radiotherapy in the management of severe Graves' ophthalmopathy: results of prospective, single-blind, randomized study. *J Clin Endocrinol Metab* 86: 3562–3567.
 18. Kubo T, Toki J, Kado Y, Kurihara M, Moriwake T, Kanzaki S, Seino Y (2000) Thyroid-stimulating antibody in a patients with euthyroid Graves' disease. *Endocr J* 47: 197–201.
 19. Watanabe M, Iwatani Y, Kashiwai T, Iijima T, Fujikado T, Amino N (1995) Euthyroid Graves' disease showing no thyroid abnormalities except positive thyroid-stimulating antibody (TSAb): two case reports. *J Intern Med* 238: 379–384.