Graves's Disease, an Unusual Complication: Raised Intracranial Pressure Due to Premature Fusion of Skull Sutures

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Graves's disease is uncommon in childhood, only 5% of the total cases falling within the age-group 0-15 years (Saxena, Crawford, and Talbot, 1964). Excluding the transient neonatal form of thyrotoxicosis, we have been able to trace only 4 cases of hyperthyroidism beginning before 2 years. The purpose of this paper is to describe a boy with Graves's disease who presented in the second year of life, and subsequently developed raised intracranial pressure from premature fusion of his skull sutures.

Case Report

A 20-month-old boy was referred to Dr. W. D. Elliott because of diarrhoea and failure to thrive. From 15 months he had had bouts of diarrhoea lasting 2 or 3 weeks during which he passed up to 6 unformed green stools daily followed by normal stools for a week or two. For about the same period he had failed to gain weight and during the month before he was seen he had lost 0.45 kg. (1 lb.). He was admitted to hospital for investigation.

He was an intelligent, nervous boy. His milestones had been normal, he sat at 5 months, said odd words at 6 months, and walked at 10 months. Psychological tests revealed a Merrill-Palmer Intelligence Scale IQ of 107 and a Vineland Social Maturity Quotient of 118. Psychological assessment showed his intellectual level to be near the top of the normal range of cognitive ability (90-110) and his social development was also high (110-119). His weight was just below the 10th centile and his height just above the 25th centile (Fig. 1a and b). There was a firm enlargement of the thyroid, with a loud bruit. The goitre was easily visible with the head slightly extended (Fig. 2). His hair was sparse. His pulse rate varied between 110 and 160/min. and did not fall below 100/min.; the blood pressure was 140/60 mm. Hg. Though several observers noted his 'stare', there was no exophthalmos or lid

retraction. The optic fundi were normal and the head circumference was 47.5 cm. which is on the 10th centile for his age. The skull shape was normal but x-ray (at 20 months) showed fusion of all skull sutures.

While in hospital he had intermittent pyrexia up to 39.4 °C. (Fig. 3). When febrile he sweated profusely but he did not seem ill. He slept soundly at night but always threw off his bed-clothes. During the day he was strikingly hyperactive and would never sit still.

On further questioning the parents revealed that there had been a personality change at about the time that the diarrhoea began. Previously a happy, equable child, he had become nervous, easily excited and frightened, and prone to temper tantrums. He was born at 37 weeks' gestation by elective caesarean section. The pregnancy had been normal except for maternal iron deficiency anaemia. His birthweight was 3175 g. and the neonatal period had been normal. His weight gain (as recorded by the Welfare Clinic he attended) had been entirely satisfactory, consistently just below the 50th centile. At 9½ months his rate of weight gain decreased and this trend was not reversed till treatment was started.

There was no family history of thyrotoxicosis, goitre, or exophthalmos, and no clinical thyroid disease could be detected in his parents or sibs.

Investigations

Thyroid investigations. Investigations confirmed that he was severely thyrotoxic. The serum $PB^{127}I$ was 16.4 µg./100 ml. The thyroid ^{131}I uptake at 6 hours was 83% of the dose, and after tri-iodothyronine 100 µg. daily for one week was 86% of the dose. The results of detailed iodine studies are shown in the Table. Simultaneous readings of thyroid ^{131}I uptake and plasma ^{131}I uptake were taken at arbitrary times determined by when he passed urine, at 2 hours 40 minutes and 4 hours 14 minutes after ingestion of the ^{131}I . The average blood radioactivity over this period was then calculated from the formula:

FIG. 1.—Weight and height charts of the patient.

$$B = \frac{B_1 - B_2}{\log_e B_1 - \log_e B_2}$$
$$= \frac{B_1 - B_2}{2.3 (\log_{10} B_1 - \log_{10} B_2)}$$

Where B = average plasma ^{131}I concentration, and B_1 = plasma ^{131}I concentration at 2 hr. 40 min. after dose; B_2 = plasma ^{131}I concentration at 4 hr. 14 min. after dose.

The thyroid and renal iodide clearances were then derived (Alexander *et al.*, 1962). The thyroid iodide

FIG. 2.—Thyroid enlargement.

clearance was 87 ml./min. (normal adult range 6.6–44.4, mean 22.7 ± 1.7 standard error), renal iodide clearance was 10.5 ml./min. (normal adult range 11.7–61.8, mean 30.5 ± 2.0 standard error). The plasma was passed through a column containing the resin IRA 400 (CI) which removed iodide. An estimate of the inorganic radio-iodide level was obtained by subtracting the effluent count from the initial count. These results are shown in the Table and Fig. 4. The plasma PB^{131}I at 24 and 48 hours was extracted with butanol (DeGroot and Stanbury, 1959) which removed 95% of the radioactivity, a normal result.

Thyroglobulin antibodies were positive in a titre of 1/15,625. A high level of long-acting thyroid stimulator (LATS) was present in the serum, there being approximately 10 milli-units of the standard per ml.

TABLE
Thyroid Investigation Results

Time After Dose ^{131}I	Thyroid Uptake ^{131}I (% Dose)	Plasma		
		Total ^{131}I (% dose per litre)	PB ^{131}I (% dose per litre)	BE ^{131}I (% of PB ^{131}I)
2 hr. 40 min.	65.2	2.1	1.5	—
4 hr. 14 min.	73	3.7	3.3	—
6 hr.	78	—	—	—
24 hr.	55	16.7	16.5	> 95
48 hr.	41.5	20.4	20.1	> 95

FIG. 3.—Pulse and temperature charts of the patient.

Other investigations. Hb 72%, PCV 34%, and MCHC 31.5%, white cells 7500/cu.mm.; differential count normal; serum iron 62 μ g./100 ml., serum cholesterol 86 mg./100 ml., plasma protein 5.6 g./100 ml., serum calcium 10.7 mg./100 ml., phosphate 4.6 mg. P/100 ml., serum alkaline phosphatase 18 KA units. ECG showed only sinus tachycardia at 145/min.; urine amino acid chromatography showed an amino-aciduria of generalized distribution; EEG was normal.

Radiological studies at 21 months showed a normal chest film, and much advanced bone age (Fig. 5)

estimated at the hand and wrist at 5½–6 years (Greulich and Pyle, 1959). Skull x-ray showed virtually total premature fusion of the sagittal, coronal, and lambdoid sutures (Fig. 6). His dental age was estimated by radiological examination as being between 24 and 30 months (chronological age 20 months).

Progress

Treatment was started at 23 months with carbimazole 30 mg. daily in divided doses. 8 weeks later he had

FIG. 4.—Thyroid ^{131}I uptake and plasma total ^{131}I , inorganic ^{131}I and protein-bound ^{131}I after a tracer dose of ^{131}I .

become clearly hypothyroid: he was sleepy, constipated, and complained of feeling cold. At that time he was conspicuously inactive, his extremities were cold, and his face was slightly puffy. He had gained 900 g. in weight since treatment was started, and the goitre had become larger (maximum neck circumference had increased from 48 to 50 cm.). The dose of carbimazole was halved and l-thyroxine in a dose of 0.2 mg. daily was introduced. A month later he was clinically euthyroid and the goitre had become slightly smaller.

At the age of 29 months having then had 6 months' treatment, his mother reported that he had had 3 episodes of vomiting with headache, each attack lasting for several days. The first of these episodes had occurred 8 weeks previously. He was found to have bilateral papilloedema. The fundi had been examined 3 months before when the optic discs were normal. During the 8 months that he had been under observation his head circumference had increased from 47.5 to 48 cm., but this small increase is within the observer error.

An air ventriculogram showed normal lateral and third ventricles. It was concluded that the papilloedema was due to raised intracranial pressure resulting from continued brain growth in the presence of premature fusion of the skull sutures. Linear craniectomies were therefore performed by Mr. L. Lassman. At operation the brain was found to be 'tight' and the sutures were completely closed. Linear craniectomies were made (in two stages with a 10-day interval) to open up the coronal, lambdoid, and sagittal sutures. Polyethylene strips were applied over the edges of the linear craniectomies and secured with clips.

His post-operative course was uncomplicated. 10 days after the second stage of the operation the optic discs were less swollen, and a month later they were completely normal. There have been no further episodes of headache and vomiting. 24 months after the beginning of treatment on the same dose of carbimazole and l-thyroxine he remains clinically euthyroid, and his weight gain and growth in height are normal.

Family Studies. No LATS was detectable in the unconcentrated sera of the parents or of the two sibs. Thyroglobulin antibodies were also demonstrated in the sera of his mother aged 36 years (titre 1/125) and his sister aged 8 years (titre 1/20) but not of his father (aged 34 years) or his brother (aged 7 years). His mother's serum also showed gastric parietal cell antibodies detected by the immunofluorescence technique. Complement-fixation tests for thyroid and gastric antibodies were negative in the whole family as were gastric intrinsic factor antibodies and antinuclear factor.

Discussion

Apart from transient neonatal thyrotoxicosis in infants born to mothers with Graves's disease (Rosenberg, Grand, and Silbert, 1963), thyrotoxicosis beginning before the third year of life is extremely rare. Hayles (1966), in a review of all

FIG. 5.—X-ray of hand and wrist showing advanced bone age (5½-6 years).

FIG. 6.—Skull x-ray at 20 months, showing virtually total premature fusion of the sagittal, coronal, and lambdoid sutures.

the cases of childhood thyrotoxicosis at the Mayo Clinic over a 40-year period, refers to one child whose symptoms started at 11 months, but no details are given about the subsequent progress. This is presumably the same child described by Helmholtz (1926) in whom hyperthyroidism was diagnosed at the age of 3 years and cured by partial thyroidectomy. At 11 months she developed diarrhoea followed by exophthalmos, tachycardia, thyroid enlargement, and loss of weight leading to emaciation. Braid and Neale (1930) described a girl with thyrotoxicosis whose symptoms first appeared after pneumonia at the age of 1 year. At the age of 2½ years after measles she became much worse. A right thyroid lobectomy was performed but she died immediately after the operation. The thyroid was uniformly enlarged and both the operation specimen and the remaining thyroid at necropsy showed diffuse hyperplasia. Elliott (1935) described a girl with exophthalmic goitre whose symptoms began when she was 6 months old. She had recurrent thyroid crises which were not adequately controlled by iodine, but after subtotal thyroidectomy at the age of 2, she became mildly hypothyroid. Finally Paterson and Gallant (1931) described a girl who had exophthalmos at the age of 4 months. At the age of 8 years exophthalmos was still present and there was clinical evidence of hyperthyroidism, which persisted at least until she was 14 (Ellis, 1935). We have found no other reports in the literature (excluding transient neonatal thyrotoxicosis) of hyperthyroidism beginning before the age of 2 years.

Detailed thyroid investigations confirmed the presence of hyperthyroidism. Labelled thyroid hormone entered the circulation at the earliest time studied (2 hours 40 minutes after the tracer dose) and by 24 and 48 hours the plasma $PB^{131}I$ had reached the extremely high levels of 16.5% and 20.1% respectively of the dose per litre. In thyrotoxic adults the highest $PB^{131}I$ level at 48 hours reported in a large series by Goodwin *et al.* (1951) was 3.4% of the dose per litre. The much higher value seen in our case could have been due to a very low intrathyroidal iodine pool, to discharge of labelled thyroid hormone into a small plasma volume, or to reduced hepatic uptake of thyroid hormone. It is not possible to decide which combination of factors was responsible in this case. Since more than 95% of the $PB^{131}I$ at 24 and 48 hours was extractable by butanol, the raised $PB^{131}I$ was not due to the iodinated albumin-like compound found in the plasma of some thyrotoxic patients (Stanbury and Janssen, 1962).

The high level of $PB^{131}I$ is also of interest because of the recent description of a positive correlation between the circulating levels of $PB^{131}I$ and LATS (Carneiro, Dorrington, and Munro, 1966). In our case both $PB^{131}I$ and LATS levels were high. The high concentration of LATS confirmed that the hyperthyroidism occurred as part of the syndrome of Graves's disease. The familial association of thyroid disease and thyroid auto-immunity has often been described (Hall, Owen, and Smart, 1960), and is particularly well marked in the families of children with auto-immune thyroid disease (Hall, Saxena, and Owen, 1962). The low titres of thyroglobulin antibodies found in the patient's mother and sister imply the presence of mild subclinical auto-immune thyroid disease.

Though the age of onset of symptoms in the boy described here was exceptionally young (15 months), his symptoms were at first characteristic of childhood thyrotoxicosis, with the usual combination of nervousness, hyperkinesia, sweating, and loss of weight in spite of increased appetite. His weight for the first 7 months of life was just below the 50th centile, but at 9½ months he was gaining less rapidly (Fig. 1). This may represent the beginning of the illness, though symptoms were not noticed until several months later. The increased rate of weight gain at the beginning of treatment is clearly shown, but his height has remained at about the 25th centile after 24 months' treatment.

One of the curious and variable features of childhood thyrotoxicosis is its effect on growth. Some children with this disorder show an acceleration of growth in height. Holmgren (1909) found that about 80% of cases under the age of 20 were above average height for their age, the acceleration of growth corresponding to the time of onset of symptoms. Similarly, Reilly (1940) found acceleration of clinical growth in 36 out of 44 children with Graves's disease, and Hung, Wilkins, and Blizzard, (1962) made the same observation in 11 out of 14 children. Greene and Singer (1965) reported greatly increased linear growth between the ages of 13 and 15 in a boy with thyrotoxicosis and Klinefelter's syndrome.

Though in the case reported here there was no acceleration of growth in height, when he was first seen at 20 months his bone age was greatly advanced to about 6 years. There was therefore a striking disparity between his growth in height which was below average and his greatly advanced bone age. Hung *et al.* (1962) have commented on this disparity in a few of their patients; out of 14 children with thyrotoxicosis 8 had an advanced bone age

and height age, 3 had an advanced bone age only, and 3 had an advanced height age only. That is to say in childhood thyrotoxicosis, height age and bone age may or may not be advanced and they appear to behave independently.

There is no information in the literature about skull size in childhood thyrotoxicosis. This boy's head circumference was slightly below average for his age, as was his height. It is suggested that the combination of the very early onset of the disease and the greatly advanced bone age, without any corresponding increase in the rate of growth of skull size, accounts for the unique features of this case, namely the premature fusion of the sutures of the skull, the subsequent development of raised intracranial pressure with papilloedema, presumably due to continuing brain growth within a skull unable to expand, and the relief of that pressure by linear craniectomies.

Summary

A boy aged 20 months presented with thyrotoxicosis. The onset of the disease may have been as early as 10 months. At 29 months, after 6 months' treatment for thyrotoxicosis, he developed raised intracranial pressure due to premature fusion of skull sutures. This was relieved by linear craniectomies.

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Donald Paterson Prize Essay

A prize essay competition will be held, open to medical practitioners registered in the United Kingdom for not more than 10 years. The value of the prize will be 25 pounds.

The subject of the essay shall be related to paediatrics but will be chosen individually by candidates. The essay shall consist substantially of unpublished work.

Entry forms and further information may be obtained from the Honorary Secretary, British Paediatric Association, Institute of Child Health, 30 Guilford St., London W.C.1. The closing date for entries will be June 30, 1969.