

# Autoimmune Thyroid Disease in Children with Mongolism

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Thyroid function in mongol children has attracted the attention of investigators for many years. Certain clinical similarities between mongolism and cretinism have led, not only to misdiagnosis, but even to the suggestion that altered thyroid function might play a part in the clinical manifestations of mongolism. Much of the earlier use of thyroid therapy in patients with this syndrome was based on this assumption. The results of thyroid function studies in patients with mongolism have been controversial; some have been suggestive of thyroid insufficiency, whereas others have been more in keeping with thyroid overactivity (Kurland *et al.*, 1957; Jackim, Wortis, and Adesman, 1961). However, most patients are clinically euthyroid, and, so far, no conclusive evidence of altered thyroid function in this group of patients has been presented.

The purpose of this paper is to report 3 cases of mongolism with coexisting hyper- or hypothyroidism, and to present the growing evidence for a relation between mongolism and thyroid autoimmunity.

## Case Histories

**Case 1.** This 7-year-old girl was admitted to the Children's Hospital in Bergen in October 1964, because of goitre, exophthalmos, and heat intolerance. She was the second child of healthy parents. The mother was 34 and the father 36 when the child was born. There was no known case of mental retardation or thyroid disorder among her relatives.

Her motor and mental development was grossly retarded, and the diagnosis of mongolism was suspected from the first year of life. The parents stated that the child had had conspicuously prominent eyes since she was 2 to 3 years of age. For the last 2 years or so before the admission, she had been intolerant to heat and sweated profusely during the night. She had not displayed any particular nervousness, fatigue, or polyphagia, and she had not lost weight. There had been no tendency to loose or frequent bowel movements.

Physical examination showed a restless child with the typical features of mongolism and hyperthyroidism (Fig.). The skin was warm and moist. There was no tremor. There was a marked exophthalmos, but no inability to converge.

Height was 117 cm. (10th centile) and weight 21.1 kg. (50th centile). Her temperature was 37.7 °C. and pulse rate 160. Blood pressure was 130/65 mm. Hg. The thyroid gland was diffusely enlarged, with firm consistency. A soft systolic murmur was heard at the left sternal border. The bone age was 6 years (Greulich and Pyle standard). Complete blood cell counts and urine analysis were normal; ESR 28 mm./hr. Serum cholesterol was 220 mg./100 ml. and protein-bound iodine 18.0 µg./100 ml. The basal metabolic rate was 145%.

Chromosome analysis gave a modal number of 46 chromosomes, with a D/G translocation. The mother was a translocation carrier, with a modal number of 45 chromosomes including a D/G translocation chromosome. The father had a normal karyotype.

The patient was treated with an initial dose of 20 mg. carbimazole administered in 3 divided doses. Within 8 weeks of treatment she was considered euthyroid and was discharged on a daily maintenance dose of 5 mg. carbimazole. This treatment was continued for 3 years. Six months after therapy was stopped she was still euthyroid. At that time the patient's and the parents' sera were tested for antithyroglobulin antibodies by the tanned red cell haemagglutination test. The patient was seropositive, with a titre of 320, whereas both parents were seronegative.

**Case 2.** This case has been reported previously without data on cytogenetics and thyroid antibodies (Lunde, 1959).

The patient was a 9½-year-old girl born in 1949. She was the fifth child of a 46-year-old mother and a 42-year-old father. During the years 1934-36 the mother received a course of x-ray therapy for thyrotoxicosis. There was no other case of thyroid disease or other endocrine disorder in the family, and no other case of mental retardation. The diagnosis of mongolism was suspected at birth, and motor and mental development were severely retarded. She had tendency to constipation since the first year of life. At the age of 5-6 years the parents noted that her voice became

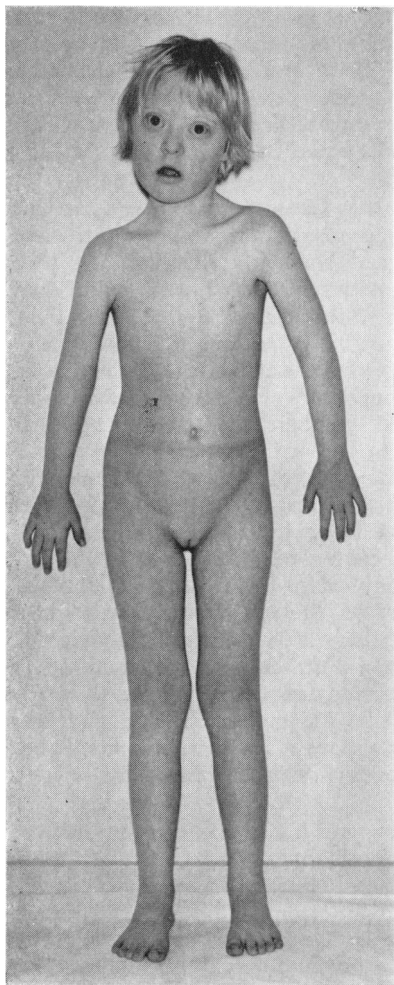


FIG.—Case 1. The features of both mongolism and hyperthyroidism are evident.

coarse, and during the past few years before admission they had been concerned about an increasing obesity. When 9½ she had a menstrual bleeding which lasted for 4 days.

On admission, she presented the typical features of mongolism. In addition, her skin was dry, scaly, and thickened, with a myxoedematous appearance. Her voice was coarse. There was no pubic or axillary hair and no breast development. Her height was 124 cm. (10–2.5 centile) and weight 45 kg. (16.5 kg. above 97.5 centile). The pulse rate was 60 and the blood pressure 90/60 mm. Hg. The thyroid gland was not palpable. Her bone age was 10 years (Greulich and Pyle standard). X-ray survey of the skeleton revealed no sign of epiphysial dysgenesis. Complete blood counts and urine analysis were normal; ESR 29 mm./hr. Serum cholesterol was 353 mg./100 ml., and protein-

bound iodine 1.9 µg./100 ml. The basal metabolic rate was 64%. After ingestion of <sup>131</sup>I the urinary excretion of radioiodine was 48% of administered dose in 24 hours.

Treatment with desiccated thyroid was started, and was followed by the disappearance of the myxoedematous features and acceleration of linear growth. She had no further menstrual bleeding before she went into normal puberty at 13½ years. Chromosome analysis showed 47 chromosomes, with 'regular' 21-trisomy. Sera from the patient and both parents were tested for antithyroglobulin antibodies by the tanned red cell haemagglutination technique when she was 19. The patient and her mother were seropositive, with titres of 80 and 640, respectively. The father was seronegative.

**Case 3.** This was a 15-month-old girl, the third child of a 42-year-old mother and a 39-year-old father. Both sibs and the parents were healthy, and there was no known case of thyroid disorder or mental retardation among relatives. Her birthweight was 3640 g. and length 51 cm. Clinical features of mongolism had been noted soon after birth, and the diagnosis was established when she was 6 months old. At that age her height was 62 cm. (10–2.5 centile). Signs of hypothyroidism were not evident. From then on a slowing of growth was noted. She was very sluggish, and her motor development was unduly slow even for a child with mongolism.

Clinical examination at the age of 15 months showed features of both mongolism and hypothyroidism. She was sluggish with a pronounced hypotonicity. She was unable to sit without support. The skin was dry and mottled and the hair sparse and dry. The voice was deep and coarse. Her height was 67 cm. (5 cm. below 2.5 centile) and weight 6.9 kg. (25–10 centile). The thyroid gland was not palpable. The abdomen was distended with an umbilical hernia. There was a considerable retardation in osseous development, and the bone age was between 3 and 6 months (Greulich and Pyle standard). X-ray survey of the skeleton did not reveal findings suggestive of epiphysial dysgenesis. Complete blood cell counts and urine analysis were normal. Fasting blood sugar 49 mg./100 ml. Serum protein-bound iodine 2.1 µg./100 ml. Chromosome analysis showed a modal number of 47 chromosomes, with one extra chromosome No. 21. At the age of 8 years her serum was tested for antithyroglobulin antibodies which were present with a titre of 80. The mother was also seropositive, whereas the father was seronegative.

Treatment with desiccated thyroid resulted in gradual disappearance of all features of hypothyroidism. She became more alert, and after an initial catch-up growth, the linear growth proceeded in a channel near the 2.5 centile.

### Discussion

At birth, the incidence of mongolism in populations of European origin is of the order of 1 in 700 (Penrose and Smith, 1966), and the prevalence

among 10-year-old children is of the order 1 in 1000 (Carter, 1958). Figures for the prevalence of hypo- and hyperthyroidism in childhood derived from the general population are not available. However, the combined frequency of these disorders in non-endemic areas is undoubtedly of a lower order than that of mongolism. The expected frequency of a combination of mongolism and thyroid disorder from chance association is therefore most probably of the order of less than one in a million. Including the present cases, a total of 12 children have been reported in whom mongolism has coexisted with hypothyroidism (Table I). The association of mongolism and hyperthyroidism has been reported in 11 children under 16 years of age (Table II). It will be noted that the majority of reports have appeared during the past decade and with increasing frequency.

As already alluded to, there is growing evidence for some association between mongolism and immunological phenomena related to autoimmune thyroid disease. The suggestion that Hashimoto's thyroiditis, or chronic lymphocytic thyroiditis, is an autoimmune disease was first presented in 1956 by Roitt and associates who showed that many patients with Hashimoto's struma had circulating auto-antibodies to normal thyroid constituents. Since then, it has been well established that lymphocytic thyroiditis is a frequent cause of goitre in children (Saxena and Crawford, 1962; Leboeuf and Bongiovanni, 1964; Nilsson and Doniach, 1964; Hahn, Hayles, and Woolner, 1965). There is a high predominance of females over males, approximately 9 to 1 (Leboeuf and Ducharme, 1966). The peak incidence of lymphocytic thyroiditis in childhood is in the early pubertal period, and usually the children are euthyroid and present with a goitre. While thyroid antibodies occur only rarely in normal children, they are regularly present in lymphocytic thyroiditis (Leboeuf and Ducharme, 1966). Though this relation does not imply that circulating antibodies directly cause the goitre and the eventual thyroid atrophy, the demonstration of such antibodies is useful in diagnosing thyroiditis in childhood. Many patients with both juvenile and adult hypothyroidism also have thyroid antibodies, and there is increasing evidence that this disorder is the end result of lymphocytic thyroiditis (Owen and Smart, 1958; Leboeuf and Ducharme, 1966). Indeed, it has been suggested that chronic lymphocytic thyroiditis is the most common cause of acquired hypothyroidism in childhood (Winter, Eberlein, and Bongiovanni, 1966). Similarly, many patients with hyperthyroidism have thyroid antibodies, and

it has been suggested that this disease may have an autoimmune basis (Anderson *et al.*, 1964). Saxena (1965) studied thyroid antibodies in 12 children with proven thyrotoxicosis and their parents. Antibodies were found in all but one of the children and in one or other parent of 10 of them.

Hereditary factors seem to play a part in aetiology or pathogenesis, since thyroid antibodies and thyroid disease are frequently found in the parents and sibs of patients (Hall, Owen, and Smart, 1960; Doniach, Nilsson, and Roitt, 1965; Foley *et al.*, 1968). Fialkow *et al.* (1965a) examined the incidence of thyroid disease in 44 families of patients with mongolism, and compared the findings with an equal number of control families from the same area and with maternal ages at the time of examination, matching those of the mongol families. Thyroid abnormality was found in 9 of 44 mothers (20%) of mongol patients as opposed to 3 of 44 (7%) of control mothers. 3 of the 9 mothers had Hashimoto's thyroiditis. 2 of 42 fathers of mongol patients had clinical thyroid disease, whereas none of the fathers in the control group was scored as abnormal. Further convincing facts were obtained when grandparents and great-grandparents were included in the evaluation, and altogether 21 of 44 (48%) mongol patients, as opposed to 9 of 44 (20%) control cases, had family histories of thyroid disease.

Fialkow and his associates went on to study the incidence of thyroid antibodies in 148 mothers of mongol children, using as controls blood bank donors from the same geographical area, matched for age (Fialkow *et al.*, 1965). 42 of 148 (28%) of the mothers of mongol children were seropositive in contrast to 21 (14%) seropositive control women. The incidence of seropositivity in mothers of mongol children did not differ significantly throughout the different age ranges, whereas the incidence in the control group increased notably with age, reaching a frequency similar to that seen in mothers of mongol patients. The most significant difference was found in the younger age-group (20-32 years) where 27% of the mothers of mongol patients were seropositive, in contrast to 4% in the control group. When the mothers were divided into two groups, i.e. a younger group who had their affected child when they were under 35 years, and an older group representing a maternal age of 35 years or over, it was found that the seropositivity was almost confined to the younger mothers (Fialkow, 1967).

Examination of thyroid antibodies in patients with Down's syndrome has been the object of

TABLE I  
Reported Cases of Mongolism Associated with Hypothyroidism

Author	Patient								Mother	
	Age (yr.)	Sex	Karyo-type	Hypo-thyroid-ism	PBI (µg./100 ml.)	Serum Choles-terol (mg./100 ml.)	Thyroid Anti-bodies	Miscellaneous	Age (yr.)	Thyroid Anti-bodies
Marañon, Martinez Diaz, and Gochi Mendizabal (1951) ..	12	M		Acqui-red ?		287		Sexual pre-cocity	40	
Talbot <i>et al.</i> (1952) .. ..	10/12	F		Conge-nital ?	1·9					
Esen and Mautner (1957) .. ..	6	F		Acqui-red		289			19	
Hubble (1963) .. .. .	5 6/12	F	Trisomy-21	Acqui-red	2·3	610		Sexual pre-cocity		
Hayles, Hinrichs, and Tauxe (1965) .. .. .	13 6/12	F		Acqui-red	1·7	295		Sexual pre-cocity	30	
Pabst, Pueschel, and Hillman (1967) .. .. .	8	F	Trisomy-21	Acqui-red	1·7		Present	Sexual pre-cocity	41	Present
Matsaniotis, Karpouzas, and Economou-Mavrou (1967) ..	6	M	Trisomy-21	Acqui-red	0·0	240	Absent	Seminoma	30	Absent
Harris and Koutsoulieris (1967)	3 10/12	F	Trisomy-21	Acqui-red	2·5	1250	Present		27	Absent
Daniels and Simon (1968) ..	17	M	Trisomy-21	Conge-nital ?	1·5			Diabetes; seminoma	49	
Litman (1968) .. .. .	1 1/12	M	Trisomy-21	Acqui-red	1·8			Diabetes	38	
Present report										
Case 2 .. .. .	9 6/12	F	Trisomy-21	Acqui-red	1·9	353	Present	Sexual pre-cocity	46	Present
Case 3 .. .. .	1 3/12	F	Trisomy-21	Acqui-red	2·1		Present		42	Present

several studies. Mellon, Pay, and Green (1963) and Robertson, Mellon, and Stewart (1965) studied 35 mongol patients in an institution, and found

thyroid antibodies in 7 in contrast to none in a group of 35 institutionalized controls matched for age, sex, and intelligence. In another series of

TABLE II  
Reported Cases of Mongolism Associated with Hyperthyroidism

Author	Mother's Age (yr.)	Patient's Age (yr.)	Sex	Karyotype	PBI (µg./100 ml.)	Serum Choles-terol (mg./100 ml.)	Miscellaneous
Dupuy and Garcia Mañrigal (1957) .. .. .		15	F			180	
Esen and Mautner (1957) .. ..	43	15 6/12	F			152	
Diggle and Weetch (1958) .. ..		6	F			130	
Nickey (1960) .. .. .		11 11/12	F		14·5	124	
Johnson and Cook (1962) .. ..	40	14	F		20·0	200	Brother juvenile myxoedema
Kay and Esselborn (1963) .. ..		9 6/12	F	Trisomy-21	10·9		
		13	F		14·5		Diabetes
		13	F		14·0		Diabetes
Hayles <i>et al.</i> (1965) .. .. .	29	14 7/12	F		11·0	113	
Šubrť, Blehová, and Kučera (1968) .. .. .	41	6	M	Trisomy-21	9·5	178	Diabetes
Present report, Case 1 .. .. .	34	7	F	D/G trisomy	18·0	220	Thyroid antibodies present

75 mongols, Fialkow and co-workers (1965b) found 13 seropositive, and 12 of them were 25 years or less. Burgio and his colleagues (1965) studied 12 mongol children and found thyroid antibodies in 7, in contrast to 3 seropositive in 48 controls. In a larger series of 50 mongol children aged 1 to 15 years, there were 14 (28%) with agglutinating antibodies to thyroglobulin (Saxena and Pryles, 1965): 30 mentally retarded children from the same institution, matched for age and sex, served as controls and thyroid antibodies were found in 2 instances (7%).

These data indicate that mongol children might have a predisposition to autoimmune thyroid disease. On the assumption that congenital and acquired hypothyroidism, and that hypo- and hyperthyroidism have the same likelihood of being reported, such a predisposition should presumably be reflected by the relative frequency of the different types of thyroid disorder. In Table III the reported cases of thyroid disorder associated with mongolism have been compared with a series of children with thyroid disease attending the Endocrine Clinic of Harriet Lane Home (Wilkins, 1965). With due reservation for the small number

TABLE III

*Frequency of Thyroid Disorders in Reported Cases of Mongol Children, Compared with Children Attending Endocrine Clinic (Harriet Lane Home)*

	23 Mongol Children	256 Children Attending Endocrine Clinic
Hypothyroidism		
Congenital	2	167
Acquired	10	45
Hypothyroidism, all types	12	212
Hyperthyroidism	11	44
Total ..	23	256

of children in the mongol group, the most striking feature is the paucity of congenital hypothyroidism in this group. This effect is in accordance with the presupposition that mongol children have a predisposition to develop autoimmune thyroid disease. The relation between the frequency of acquired hypothyroidism and hyperthyroidism seems to be similar in the two groups of children. There is a preponderance of females both in acquired hypothyroidism (Table I), and especially in hyperthyroidism (Table II). The latter finding is in accordance with that observed in two larger series of children with hyperthyroidism. In a

series from the Mayo Clinic, the ratio of females to males was 6 to 1 (Hayles *et al.*, 1959), and in Wilkins' (1965) series from the Harriet Lane Home the ratio was 4 to 1. The ratio in this small series of mongol children is closer to the 9 to 1 ratio observed in children with lymphocytic thyroiditis. Thyroid antibodies were seen in 4 of 5 cases of acquired hypothyroidism tested and in 3 of the 5 mothers. Only one child in the hyperthyroid group was tested for thyroid antibodies, and she was seropositive, whereas both parents were seronegative. 3 of the children with hyperthyroidism had a family history of thyroid disorder. In the hypothyroid group, there were statements on thyroid disorders in the family in 5 of the reported cases, and a positive history in 2 of them: 2 of the children in the hypothyroid group and 3 in the hyperthyroid had concomitant diabetes mellitus in addition to thyroid disease and mongolism. This is noteworthy because of the raised incidence of thyroid antibodies and Hashimoto's thyroiditis in patients with diabetes (Landing *et al.*, 1963; Moore and Neilson, 1963).

An increased incidence of autoimmune thyroid disease and thyroid antibodies has also been observed in Turner's syndrome. Originally this association was thought to be limited to patients with gonadal dysgenesis and X-isochromosome (Engel and Forbes, 1961; Sparkes and Motulsky, 1963; Grumbach and Morishima, 1964). However, subsequent work has shown that patients with Turner's syndrome and their parents have a higher incidence of thyroid antibodies than controls, and that there is no correlation between these findings and the karyotype of the patient (Vallotton and Forbes, 1967). Since neither the mechanism giving rise to auto-antibody formation, nor that responsible for chromosomal abnormalities is known, there are two possibilities that would explain the association of the two phenomena. Chromosomal disorder could be primary and existing chromosomal anomalies might give rise to auto-immunity. Alternatively, auto-immunity or a related factor may predispose to chromosomal aberration. The latter hypothesis has in particular been advocated by Fialkow (1966). The high frequency of thyroid antibodies in mongol patients and in those with gonadal dysgenesis does not seem simply to be the result of their chromosomal abnormalities, since the parents, who do not themselves have such abnormalities, also have a high incidence of autoimmunity when compared with age-matched controls. It is well known that females have a higher incidence of circulating auto-antibodies and a higher incidence of most of

the disorders which are associated with them than males. It is also well documented that the incidence of auto-antibodies increases with increasing age. These factors are relevant in mongolism, since the non-disjunctional event leading to this disorder has a clear relation with advanced maternal age. However, advanced maternal age is not related to the XO Turner syndrome, and non-disjunction has more often been traced to the paternal than to the maternal X chromosome (Lindsten *et al.*, 1963).

Chromosome analysis in patients with mongolism and thyroid antibodies has shown both regular trisomy-21 and the more unusual karyotypes. In one series with 7 seropositive patients, there was one with normal/trisomy-21 mosaicism, one with D/G translocation, and one with G/G translocation (Robertson *et al.*, 1965). It is of interest that mosaicism has also been found in 3 patients with mongolism whose mothers had Hashimoto's thyroiditis and/or thyroid antibodies (Fialkow, 1967). Chromosome analysis has been carried out in 8 of the cases with mongolism associated with acquired hypothyroidism, and all of them showed regular trisomy-21 (Table I). Only 3 children in the hyperthyroid group were karyotyped: 2 of them had regular trisomy-21. The third, Case 1 in the present report, showed an inherited D/G translocation, and is of particular interest in the discussion of whether the thyroid antibodies, or a factor related to them, cause the chromosomal abnormality, since the child was seropositive whereas the mother, who was the D/G translocation carrier, was seronegative.

In conclusion, there is a fair amount of circumstantial evidence that mongolism and thyroid autoimmune disease are associated, but the role of thyroid autoimmune phenomena in causing chromosome aberrations is at present uncertain.

### Summary

Three girls with mongolism associated with thyroid disorder are reported. One child had hyperthyroidism, and the other two had acquired hypothyroidism. One of the latter had precocious menstrual bleeding at the age of 9½ years. Chromosome analysis showed regular trisomy-21 in both children with hypothyroidism, and thyroid antibodies were present in both the mothers and the children. The child with hyperthyroidism had D/G translocation trisomy, and thyroid antibodies were present in her serum, whereas the mother who was D/G translocation carrier was seronegative.

A total of 11 children including the present cases, have been reported with the combination of

mongolism and hyperthyroidism. The association with hypothyroidism has been reported in 12 children, and only 2 of them had congenital hypothyroidism.

There is growing evidence to support the suggestion that there is an association between mongolism and thyroid autoimmune disease.

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