Endocrine abnormalities and myopathy in Bloom's syndrome

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SUMMARY Abnormal endocrine indices and myopathy have been variably present in two brothers with Bloom's syndrome (congenital teleangiectatic erythema, hypersensitivity to light, and growth retardation). These consisted of: (1) growth retardation with height and weight below the third centiles; in the younger one at age 14, hypoglycaemia failed to elicit a rise in growth hormone but did so in the older one at age 17; (2) serum TSH was raised in the older one in whom serum FSH and LH were also above the normal range; and (3) myopathy characterised by pronounced dilatation of the sarcoplasmic reticulum was present in the younger one; distinct reduction of muscle strength was shown in his older brother with ultrastructural alteration of skeletal muscle of unknown significance.

Bloom's syndrome (Bloom, 1954a, b; Szalay, 1963; Bloom, 1966; Sawitsky *et al.*, 1966; Schoen and Shearn, 1967; German, 1969, 1972, 1974) is an autosomal recessive inheritable disorder characterised by teleangiectasia, hypersensitivity to sunlight, growth retardation *in utero* and thereafter, and chromosomal aberrations with quadricentric (Qr) forms. More than one-half of cases have appeared in Ashkenazik Jews as well as in offspring of consanguineous unions (Bloom, 1954a; German, 1974). Other congenital anomalies of the ears, teeth, and extremities have been observed as well as an increased propensity of these individuals to develop neoplastic disease. Weakened, delayed, or absent hypersensitivity responses, hypogammaglobulinaemia, as well as frequent respiratory and gastrointestinal infections have been noted (German, 1974). Though occasional cryptorchidism (cases 3, 4, and HC in Bloom, 1954a) and one instance of aspermia (German, 1974) have been encountered, no other endocrinopathy, except possibly the stunting, has been observed.

This report concerning two brothers with this entity who earlier had been reported as cases 3 and 4 in Bloom's series (1954a) discloses the absence of a growth hormone response to hypoglycaemia in one and high serum thyroid stimulating hormone (TSH) and increased levels of serum follicle stimulating and luteinising hormones (FSH and LH) in the other.

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These findings suggest that endocrinopathy may develop with increasing age in these patients. In addition, muscle weakness was present in one of the two brothers, with pronounced dilatation of sarcoplasmic reticulum in the other.

Clinical findings

The history of these two brothers at the age of 4 years and 7 years, respectively, has been previously reported by Bloom (1954a). Subsequent to that publication, the younger patient (LS), now age 16 years, has failed to grow at a normal rate and has been found to have an IQ of less than 90. He experienced frequent respiratory infections including two episodes of pneumonia and has taken prophylactic antibiotics for infections.

The older brother (CS), now age 18 years and 11 months, also failed to grow normally and has a 'dull-normal' IQ. He failed three school grades. He also had respiratory infections, though less frequent and less severe than those of his brother. He suffered from severe photophobia.

Physical examination showed that both were below the third centile for height and weight. Both had facial telangiectasia and desquamation, moderate in the younger and more severe involving all of the face in the older one. The lips were dry and desquamating in each. Partial syndactyly was present in the second and third toes of both feet in the two patients. The

testes measured 2.5 cm in length in both patients and the penis was commensurate with body size. Pubic hair was present only in the older brother who also had clubbing of the fingers.

Laboratory findings

Blood and serum solutes, including liver indices and lipids, were within the normal range in both patients. Oral glucose tolerance test was normal. Thus, ingestion of 1.75 g glucose per kg body weight yielded a normal glucose tolerance sum (GTS_{0-2hr}—sum of the blood glucose values at 0, ½, 1, and 2 hours) of 406 (Danowski *et al.*, 1970). In the older sib, the GTS_{0-2 hr} value was also normal at 416. This was also true of creatinine clearance and urinary 17-ketosteroids, Porter-Silber chromogens, and 11-desoxycortisol metabolites.

Skull and chest x-rays were negative. Bone age in the younger brother was three years below the chronological age; in the older, bone age was one year above the chronological age. Electrocardiogram tracings were normal and urine analyses were negative. In the younger boy, 7% eosinophilia was noted in the peripheral blood smear. The remainder of the peripheral blood count was normal in both.

Endocrine findings, with one exception, were normal in the younger of the two brothers. In the younger brother, the fasting growth hormone levels were less

than 1 ng/ml at age 13 and did not increase during insulin-induced hypoglycaemia (Table 1). One year later, the fasting growth hormone level was 4.0 ng/ml. Plasma cortisol was 10 γ% in the morning and 5 in the afternoon. This younger patient responded to intravenous leutinisising releasing hormone (LRH) with a rise in serum FSH from 9 to 18 mIU/ml in 3 hours with corresponding LH values of 5 and 50 mIU/ml (Table 2). The basal testosterone level was 195 ng/100 ml. He also responded to intravenous thyroid-releasing hormone (TRH), with a rise in serum TSH from 10 to a peak of 32 μIU/ml at 30 minutes; and within the same period, prolactin increased from 7 to 12 ng/ml. In addition, 3 hours after the TRH, serum triiodothyronine measured by radioimmunoassay (RIA-T₃) had increased from 150 to 220 ng/100 ml.

The older sib responded adequately to insulin-induced hypoglycaemia, that is the growth hormone rose from 1 ng/ml to 48 ng/ml at 30 minutes. He had increases in basal serum TSH to more than 100 μIU/ml (normal range 2 to 10) and normal RIA-T₃ of 160 ng/100 ml and RIA-T₄ of 7 γ%. In addition, his serum FSH was increased at 26 and at 22 mIU/ml when measured 4 weeks apart with corresponding LH values of 25 and 36 mIU/ml. Serum testosterone was 420 and 658 ng/100 ml at these times (normal 400 to 1000). Plasma cortisol was also normal at 20 γ% in the morning and 14 in the afternoon.

Chromosome analysis of short-term cultures of blood lymphocytes of each patient disclosed quadri-radial (Qr) configuration of E group homologues indicative of multiple chromosome breakage and rearrangement of the type reported in Bloom's syndrome (Sawitsky *et al.*, 1966; German, 1969, 1972, 1974; German *et al.*, 1974; Schroeder and German, 1974; Hand and German, 1975).

Performance on recording ergometry (105 consecutive contractions of each hand at 1 s intervals) was normal in the younger patient but revealed a pronounced decline of excursions in the older one. Serum creatine kinase (CK) and aldolase were normal at 36 and 4 units, respectively, in the younger brother; but CK was raised to 123 units in the older brother. Motor nerve conduction velocity was normal in the median, ulnar, common peroneal, and posterior

Table 1 Intravenous insulin (0.1 unit/kg body weight) tolerance tests

Patient	Index	Time				
		0	15'	30'	60'	120'
LS	Blood glucose (mg/100 ml)	74	30	56	58	70
	Serum insulin (uU/ml)	<1	398	42	<3	<3
	Serum growth hormone (ng/ml)	<1.0	<2.5	<2.5	<2.5	<2.5
CS	Blood glucose (mg/100 ml)	74	30	47	45	76
	Serum insulin (uU/ml)	38	34	87	21	12
	Serum growth hormone (ng/ml)	<1.0	<2.5	31.2	39.2	48.5

Table 2 LRH (50 γ N in 4 h), TRH (500 γ bolus), and ACTH (cortrosyn, 0.75 mg bolus) in patient LS

Serum	TIME						
	0	15'	30'	1°	2°	3°	4°
Prolactin (ng/100 ml)	6.8	12.4		5.6	4.5	7.0	2.5
TSH (μIU/ml)	9.7	32.5	28.5	18.0	9.5	5.5	5.0
RIA-T ₃ (ng/100 ml)	150						220
FSH (mIU/ml)	8.6	9.7	14.9	9.8	13.0	18.0	18.4
LH (mIU/ml)	5.4	>50	>50	>50	>50	>50	>50

Fig. 1. Electronmicrograph of portion of muscle from the older sib. There is myofibre disruption with clumping of mitochondria. The latter are large and pleomorphic. Though such foci may be found in 'control' specimens, they appeared to be more numerous in this patient ($\times 9300$).

Fig. 2. Electronmicrograph of portion of muscle from the younger brother. There is pronounced dilatation of the sarcoplasmic reticulum like that observed in periodic paralysis ($\times 11\,900$).

tibial nerves in both. Electromyographic examinations were negative.

Electron microscopical study of the needle biopsy of the quadriceps femoris muscle from the older sib showed fragmentation of myofibers (Fig. 1). Mitochondria in such foci were clustered, large, and pleomorphic. Portions of endoplasmic reticulum, glycogen particles, and tubules of the 't' system were also evident in areas of myofibre disruption. The biopsy from the younger brother showed a lesser degree of myofibre alteration. Mitochondria appeared comparably altered. However, noteworthy in the biopsy from this younger sib was the pronounced dilatation of the sarcoplasmic reticulum (Fig. 2).

Discussion

German (1974) has pointed out several reasons why study of Bloom's syndrome is desirable even though only two or three affected persons are recognised

each year. First, Bloom's syndrome shows a simple recessive transmission which indicates that a single gene, *bl*, and a single enzyme is affected. The major manifestation of the gene *bl*, when homozygous, is growth retardation.

A second feature of interest is excessive chromosome instability ('breakage'). This suggests that the affected enzyme exerts its effect, directly or indirectly, on the genetic material itself, in this case, the chromosomes.

In addition, persons with Bloom's syndrome are at a greatly increased risk with respect to leukaemia and gastrointestinal and other cancers. As yet there is no evidence of neoplastic disease in the patients reported herein.

Finally, previous reports and our data establish that variable endocrinopathy can be a feature of Bloom's syndrome.

At first the absence of endocrine stigmata in the early published reports of Bloom's syndrome, the

generally normal or only slightly retarded bone age, and the normal glucose tolerance, urinary 17-ketosteroids, and gonadotropins appeared to exclude endocrinopathy (Bloom, 1954a) other than that possibly responsible for the growth retardation. Furthermore, necropsy in one patient showed normal parathyroids, ovaries, and adrenals (Bloom, 1954a; Sawitsky *et al.*, 1966). Moreover, recently German has reported that in women menarche and menses have been unremarkable (German, 1974). However, none of the three married men in his prospective study of Bloom's syndrome has had children, and evaluation of one revealed aspermia. He also reported that the testes of the adults in his series appeared to be 'disproportionately small'.

Findings in the older of the two patients whom we have restudied indicate that he had hypergonadotropic hypogonadism with high serum FSH and LH and that this was accompanied by increased levels of circulating TSH. These findings suggest gonadal and thyroidal failure but could reflect, alternatively, disturbances of the hypothalamus and/or pituitary. In the younger brother, both the gonadotropins and TSH levels were normal, but hypoglycaemia failed to evoke a rise in growth hormone. It is possible of course that hypoglycaemia was not an adequate stimulus in this patient. None the less, these findings suggest that in this entity, endocrinopathy such as growth hormone unresponsiveness present at an earlier age subsequently disappears. On the other hand, abnormalities of other endocrine indices such as increases in FSH, LH, and TSH may develop with increasing age.

The muscle biopsy of the older brother indicated abnormalities of the mitochondria and myofibres (Fisher and Danowski, 1974). The alterations observed in the biopsy from the younger brother, notably dilatation of sarcoplasmic reticulum, has not been encountered in control specimens and is a valid pathological change. Indeed, the appearance of the muscle is indistinguishable from that observed in familial periodic paralysis (Danowski *et al.*, 1975). Muscle weakness and the associated myopathy have not been cited in previous reports of Bloom's syndrome.

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