CASE REPORTS

Turner's syndrome with coeliac disease, thin bones and abnormal liver function tests

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Summary

A patient is described with 45 XO Turner's syndrome and thin bones. It transpired that the patient had osteomalacia due to gluten sensitive enteropathy rather than the osteoporosis usually expected with Turner's syndrome. In addition, she had unexplained liver dysfunction. Causes for thin bones other than the osteoporosis associated with ovarian agenesis should be considered in patients with Turner's syndrome.

Introduction

Thin bones have often been described in Turner's syndrome and are usually ascribed to osteoporosis (Haddad & Wilkins, 1959; Finby & Archibald, 1963; Lemlie & Smith, 1963; Goldberg *et al.*, 1968; Preger *et al.*, 1968). We now report a proven case of Turner's syndrome with thin bones who also had intestinal malabsorption, evidence of osteomalacia and abnormalities of liver function.

Case report

A 30-year-old woman was admitted in 1971 for investigation of thin bones seen on X-ray of a sprained ankle. At birth she weighed 3.4 kg but subsequent weight gain was slow and there were bouts of diarrhoea throughout childhood. By the age of 9 years she was 102.5 cm tall and weighed 17.8 kg, each well below the 3rd percentile. The bone age at the wrist was approximately 6 years and her haemoglobin was 8.6 gm/100 ml, but fell to 7.5 gm/100 ml over the next 3 years. At this time she was regarded as a case of pituitary infantilism, and her height remained below the third percentile. At the age of 24 years she measured 135 cm and complained of primary amenorrhoea and lack of secondary sexual development. She was given cyclical replacement therapy, menstruated and showed some breast

growth. In 1967, aged 27 years, she was first investigated at St Bartholomew's Hospital. At this time she was 137.5 cm tall, weighed 41.2 kg and the body proportions were normal. She had no gastrointestinal symptoms and no bone pain. The phenotype suggested Turner's syndrome with dwarfism, low set ears and posterior hair line, a short neck and a wide forearm carrying angle but there was no webbing of the neck. Culture of peripheral blood lymphocytes showed a 45 XO karyotype and no mosaicism in the forty cells examined. The thyroid function was normal as were the growth hormone and plasma corticosteroid responses to insulin-induced hypoglycaemia. X-ray examination showed a bone age at the wrist of 16 years, generalized thinning of the bones without any fractures or pseudo-fractures. There was abnormal modelling of the lower end of the radius and ulna and enlargement of the medial condyles of the femora with deepening of the medial portions of the tibial tables as described in Turner's syndrome (Kosowicz, 1959; Finby & Archibald, 1963; Preger *et al.*, 1968). Gynaecography showed a small uterus and very small gonadal shadows. The haemoglobin was 12 gm/100 ml, and the liver function tests were as in Table 1. The serum calcium (9.3 mg/100 ml), phosphorus (3.8 mg/100 ml), blood urea and electrolytes were normal. The mean faecal fat excretion on a 70 g fat diet was 3.6 gm/day over a 3-day period. At this time the thin bones were ascribed to the Turner's syndrome and it was thought possible that the abnormalities in the liver function tests were due to oestrogen therapy (ethinyl oestradiol) and this was discontinued. Although the alkaline phosphatase and aspartate-transaminase levels fell they did not become normal (Table 1).

On re-admission in January 1971, the X-ray appearances of the bones were unchanged and there was no evidence of hyperparathyroidism. The alkaline phosphatase, 5-nucleotidase and aspartate

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TABLE 1. Liver function tests

	serum bilirubin (mg/100 ml)	serum alkaline phosphatase (KA u/100 ml)	serum 5 ¹ -nucleotidase (iu/l)	serum aspartate transaminase (iu/l)	BSP % retention at 45 min
1967	1.4	46	—	156	5
1971					
January	0.8–1.2*	30–37*	67–72*	50–98*	5
August	0.4	25	71	72	—
November	0.8	28	89	120	—
1972	0.7	27	46	58	—
Normal range	<1.2	3–13	2–17	10–40	<5

Serum total proteins, albumin, globulin and electrophoresis were normal.

* Range of 3 or 4 estimations.

The gluten free diet was started in mid-February 1971.

Serum albumin gm/100 ml			
1967		4.7	4.5
1971	Jan	4.9	4.3
	Aug	4.5	4.4
	Nov	4.2	
1972		4.3	

transaminase were still raised but the other liver function tests were normal, see Table 1. The serum calcium and phosphate were normal (9.7–10.0 and 3.5–4.3 mg/100 ml respectively). The haemoglobin was 12.7 gm/100 ml, the blood film, indices and ESR were normal as were the serum B₁₂, iron and total iron binding capacity, urea, electrolytes and creatinine clearance. However, the serum folate was low: 0.7–0.9 ng/ml (normal range 4–18 ng/ml), the red cell folate was low: 46 and 56 ng/ml (normal range 160–640 ng/ml) and the bone marrow showed evidence of megaloblastic erythropoiesis with absent iron stores. The patient had normal stools containing 0.9 gm/day fat whilst on a 100 gm fat diet but the xylose tolerance test was abnormal, the plasma concentration being 5.7 mg/100 ml at 90 min with a urinary excretion of 4.3 gm in 5 hr (normal more than 30 mg/100 ml in plasma at 90 min and more than 4.5 gm in urine in 5 hr after 25 gm oral load) and the urinary calcium excretion was reduced, varying between 64 and 112 (mean of four collections: 100 mg/24 hr). In view of the reduced xylose tolerance, low serum and red cell folate and marrow appearance it seemed likely that the patient had malabsorption and so a jejunal biopsy was performed and this showed subtotal villous atrophy consistent with coeliac disease (Fig. 1). Liver scan and biopsy were normal as were cholecystography, cholangiography, barium meal and follow through examination.

The possibility of osteomalacia was considered and the strontium space was measured as an index of the miscible calcium pool. It was elevated (22

plasma units, normal range 12–18 units) consistent with osteomalacia (Melvin *et al.*, 1970). The origin of the alkaline phosphatase was investigated by Dr D. W. Moss; starch gel electrophoresis and heat stability measurements showed a single type of enzyme activity which was predominantly of liver rather than bone or intestinal type. Bone biopsy was obtained under local anaesthetic from the left ileum. Undecalcified sections showed trabeculi of normal width but with significant excess of osteoid indicating osteomalacia.

The patient was placed on a gluten free diet and after 9 months the red cell folate was normal (170 ng/ml), as were the xylose tolerance (serum xylose 41 mg/100 ml 90 min, 4.9 gm excreted in urine in 5 hr), urinary calcium excretion (200 and 150 mg/24 hr) and strontium space (15 plasma units). The jejunal biopsy showed considerable improvement with new villous formation. However, the alkaline phosphatase, 5¹-nucleotidase and aspartate transaminase levels remained elevated (Table 1). The patient felt better in herself. Her height was unchanged.

Family history

Father's height 179 cm, mother's height 161.5 cm; her one brother was normal. Her paternal aunt and cousin both have coeliac disease.

Comment

The patient has been shown to have Turner's syndrome with thin bones, gluten sensitive enteropathy and also liver dysfunction as indicated by the

FIG. 1. Jejunal biopsy showing subtotal villous atrophy consistent with coeliac disease.

elevated hepatic enzymes in the serum. The nature of the liver disease is unclear as the liver biopsy, scan and cholangiogram were normal.

Osteoporosis has been described often in patients with ovarian dysgenesis. Although the thin bones have been ascribed to oestrogen deficiency (Albright *et al.*, 1942; Levin, 1962; Greenblatt *et al.*, 1967), this seems unlikely to be the whole explanation as osteoporosis can be found in children with Turner's syndrome (Lemlie & Smith, 1963; Greenblatt *et al.*, 1967; Goldberg *et al.*, 1968).

Coexisting Turner's syndrome and coeliac disease does not appear to have been described before. This coincidence raises the possibility that the patient's thin bones could, in part, be due to osteomalacia. This suggestion is supported by the elevated strontium space which is abnormal in osteomalacia (Melvin *et al.*, 1970). Surprisingly, the elevated alkaline phosphatase appeared to originate from the liver, not the bones or gut. We have been unable to discover reports of established liver disease in association with either Turner's syndrome or coeliac disease and we must conclude that it is probably an independent abnormality in this patient as there has been no improvement in liver function during the 18 months that she has been followed on her gluten free diet despite the improvement in red cell folate,

the jejunal biopsy, urinary calcium, strontium space and xylose tolerance tests.

We conclude, therefore, that the patient has 3 separate conditions—45 XO Turner's syndrome, gluten-sensitive enteropathy and liver dysfunction, and can find no evidence that these are interdependent. Causes for thin bones other than the osteoporosis associated with ovarian agenesis should be considered in patients with Turner's syndrome.

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Triplets—one ectopic, two intrauterine

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Summary

A case of ovarian ectopic conception, complicating a simultaneous twin intra-uterine pregnancy is described, in which the operative diagnosis was confirmed by histological examination.

Such cases are extremely rare and comment is made upon this with references.

A 32-year-old para 4+0 was referred on 21 October 1970 for gynaecological opinion with a history of 37 days amenorrhoea and intermittent, severe right lower abdominal pain for the previous fortnight. Her last menstrual period was on 12 September 1970. She was not sure whether she was pregnant. Her appendix had been removed 13 years ago. On examination, her general condition was good. There was marked tenderness in the right iliac fossa and both vaginal fornices. A pregnosticon test done that day was negative. A presumptive diagnosis of ectopic pregnancy was made and blood was cross-matched. An examination under anaesthesia on 23 October 1970 revealed a soft uterus about the size of an 8–10 week pregnancy. On a spiration of the Pouch of Douglas about 20 mls of fresh unclotted blood was obtained. At laparotomy 60–70 mls of both fresh and old unclotted blood was found in the pelvis. The uterus was soft and enlarged to about 10 weeks gestation, which was bigger than the period of

amenorrhoea (6 weeks approx.). The right fallopian tube was enlarged, and oozing small blood clots from the fimbrial end mixed with small bits of tissue. The right ovary had a small area of old blood-clot adherent to it. A corpus luteum could not be identified. A right salpingectomy and resection of the haemorrhagic part of the right ovary was done. Histology from the ovarian tissue reported 'fragments of blood-clot, some fresh, some showing inflammatory infiltration and some of it undergoing organization and haemosiderin deposition, probably representing the contents of a ruptured corpus luteum, since some of the fragments are covered by a layer of cells resembling those lining a luteal cyst. In one section there are a few degenerate chorionic villi, confirming the diagnosis of ectopic pregnancy'. Histology report from the tubal specimen showed 'the lumen of the fallopian tube filled with blood. Scattered collections of decidual cells could be seen in many of the mucosal papillae, but no trophoblastic elements were seen in or around the fallopian tube'.

Following operation she made a good recovery. The pregnosticon test was repeated on 26 October 1970, 5 days after the first negative test, and was now positive. She was booked for hospital confinement and the uterus continued to enlarge. An Ultrasonic Scan done 4 weeks after the laparotomy reported an