Syndrome of the month

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Winchester's syndrome

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In 1969 Winchester *et al*¹ described two Puerto-Rican sisters aged four and 12 years, the offspring of first cousins, as having "a new acid mucopolysaccharidosis with skeletal deformities simulating rheumatoid arthritis". Brown and Kuwabara² described the same sibs from the ophthalmological point of view at the ages of five and 13 years. Hollister *et al*^{3,4} reported two sisters and a male cousin from an inbred Mexican kindred with a similar condition. A further similar male case was reported from Bombay by Irani *et al*.⁵ Again, the parents were first cousins. Dunger *et al*⁶ reported two cases with features similar to Winchester's syndrome with increased urinary oligosaccharide excretion. In a note added in proof it was mentioned that the first case had features similar to infantile systemic hyalinosi, a condition that is discussed under differential diagnosis below.

The purpose of this paper is to review the clinical, radiological, and pathological features of the reported cases of Winchester's syndrome, to discuss the variability and possible heterogeneity of the condition, and to clarify the differential diagnosis.

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Clinical features (table)

ONSET

In the original report of Winchester *et al*¹ onset was in the first two months of life in the first sib. Symptoms were limitation of movement of the knees and spine and painful enlargement of the wrists and proximal interphalangeal joints. In the second sib definite symptoms were noted at 20 months. In the cases described by Hollister *et al*^{3,4} and Irani *et al*⁵ onset was similarly in the first year of life. Case 2 of Dunger *et al*⁶ developed pain, swelling, and deformity of the small joints of the hands from one year (fig 1).

CRANIOFACIAL ABNORMALITIES

In the cases of Winchester *et al*¹ the facial features appeared to coarsen from around 20 months in one case and there was marked facial coarsening in the other case at eight years. The lips were thickened, the nose large and fleshy with a depressed bridge, and the forehead prominent. Cases 1 and 2 of Hollister *et al*³ were said to have thickened, leathery facial skin, the forehead was broad, and the nose short and anteverted. Case 3 had significant facial

TABLE Clinical features of cases of Winchester's syndrome.

Features	Winchester <i>et al</i> ¹		Hollister <i>et al</i> ^{3,4}			Irani <i>et al</i> ⁵	Dunger <i>et al</i> ⁶
	Case 1	Case 2	Case 1	Case 2	Case 3	Case 1	Case 2*
Sex	F	F	F	F	M	M	F
Age (y)	12	4	9½	8	22	4	16
Facial skin thickened	—	—	+	+	+	—	—
Skin nodules	—	—	+	—	—	—	—
Hyperpigmented patches	—	—	+	+	+	+	—
Coarse face	+	+	—	—	+	—	+
Corneal opacity	+	+	+	+	+	—	—
Gum hypertrophy	+	+	+	+	?	—	+
Flexion contractures	+	+	+	+	+	+	+
<i>Radiographs</i>							
Osteoporosis	+	+	+	+	+	+	+
Carpal/tarsal osteolysis	+	+	+	+	+	+	+

*Additional clinical details obtained from re-examination by present author.

(a)

FIG 1 (a) Hands of 16 year old girl with Winchester's syndrome (case 2 of Dunger *et al*⁶).

(b) Radiographs of the hands of the above case taken at 14 years.

(b)

coarsening at 22 years. The facies of the cases described by Irani *et al*⁵ were not considered remarkable at the age of four years. Case 2 of Dunger *et al*⁶ was not reported to have an abnormal face at seven years, but there was mild facial coarsening at 16 years on review by the present author.

Gum hypertrophy is reported in the majority of cases. Corneal opacities, where present, are first noted between two and five years. They first appear peripherally and progress. In the cases of Hollister *et al*³ they were noted to be in Descemet's membrane superiorly and inferiorly.

SKIN

Skin abnormalities were not reported by Winchester *et al*.¹ The cases reported by Hollister *et al*³ and Irani *et al*⁵ had patches of thickened, hyperpigmented, leathery skin on the trunk and arms. One case had a 2 cm pigmented nodule over the thoracic spine. Generalised hirsutism or patches of hair on the limbs or trunk may also be a feature.

Course of the disease

Joint stiffness and contractures are progressive and lead to clawing of the hands, flexion of the limbs,

and difficulties with walking. Both height and weight progressively fall below the third centile. Hepatosplenomegaly is not a feature of the disease. Intelligence is normal.

Radiological features

The hallmark of the disease is severe generalised osteoporosis with progressive carpal and tarsal osteolysis (fig 1b). The long bones are severely undermineralised with cortical thinning (fig 2). The metaphyses become expanded, the epiphyses flattened and irregular, and there may be ankylosis of the large joints. The tubular bones of the hands and feet broaden and there are extensive erosions involving the interphalangeal and metacarpo/tarso-phalangeal joints. In older patients the proximal metacarpals and metatarsals become resorbed and there is bony ankylosis of the phalanges. Kyphoscoliosis, compression of vertebral bodies, and instability of C1 on C2 can occur.

FIG 2 Radiograph of femur of case 2 of Dunger *et al*⁶ at 14 years.

Pathogenesis

Pathological investigations have been conflicting. Winchester *et al*¹ thought their cases had a form of mucopolysaccharidosis. This was based on the findings of metachromasia in cultured fibroblasts and increased intracellular uronic acid shown histochemically. Hollister *et al*³ found focal areas of fibroblastic proliferation which replaced the normal heavy collagen bundles in the dermis of areas of leathery skin in younger patients. In their 22 year old patient there were irregular swirling masses of abnormal collagen with hypocellularity. The carpals in one patient were replaced by dense fibrocollagenous tissue and the small and medium arterioles had undergone marked medial hypertrophy. No evidence of abnormal lysosomal storage was found on electron microscopy.

Dunger *et al*⁶ found an abnormal urinary oligosaccharide pattern in their patients. The abnormal oligosaccharide was a trimer with one fucose and two galactose residues. These findings are confusing because those of Hollister *et al*³ suggest an abnormality of fibroblasts or collagen synthesis, whereas those of Dunger *et al*⁶ suggest a problem with oligosaccharide metabolism. The situation is further confused because Dunger *et al*⁶ found the abnormal oligosaccharide in both their patients, but the first case most likely had infantile systemic hyalinosi, a separate disease. Repeat oligosaccharide analysis of the second patient reported by Dunger *et al*⁶ with apparent Winchester's syndrome has not confirmed any abnormality (B Winchester, 1989, personal communication) and skin biopsy in the same case has not shown features of infantile systemic hyalinosi (B D Lake, 1989, personal communication).

Differential diagnosis

The condition must be differentiated from storage disorders causing coarsening of the facies and severe joint diseases, such as Farber's disease and Scheie's syndrome. The radiological features can resemble severe juvenile rheumatoid arthritis in the early stages.

Patients with idiopathic multicentric osteolysis have osteolysis of the carpals and tarsals with osteoporosis, but onset is usually later in childhood, nephropathy is an associated finding, and most families show autosomal dominant inheritance. Torg *et al*⁷ described three brothers with first cousin parents with an autosomal recessive form of carpal and tarsal osteolysis, osteoporosis, and widening of the metacarpals and phalanges. Onset was at two to five years of age. Tender subcutaneous nodules around the joints and hyperpigmented and

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erythematous cutaneous lesions were additional features. This condition seems to have many similarities to Winchester's syndrome.

Landing and Nadorra⁸ described a condition called infantile systemic hyalinosis in four infants, two of whom were sibs. The main features were early thickening and focal nodularity of the skin leading to reduced movement and joint contractures, gum hypertrophy, and osteoporosis. The infants failed to thrive and had diarrhoea and recurrent infections. Onset was in the first week and death occurred before 20 months. Pathological examination showed widespread deposits of hyaline material in skin, skeletal muscle, gastrointestinal tract, endocrine glands, and other locations. The condition was probably first described by Nezelof *et al.*⁹ Carpal and tarsal osteolysis was not reported as a major feature of infantile systemic hyalinosis, and it is confusing that case 1 of Dunger *et al.*⁶ who had clinical and histological features of this condition, was said to have extensive resorption of the carpal bones. However, review of the original radiographs of this case shows osteoporosis with delayed development of the carpal bones, but with no direct evidence for osteolysis of the carpals (C Hall, 1989, personal communication).

Genetics

The reporting of two sets of affected sibs with parental consanguinity^{1,3} strongly supports autosomal recessive inheritance.

Conclusions

The cases reported as having Winchester's syndrome have varying combinations of clinical features and it is possible that the phenotype is heterogeneous. For example, the original cases reported by Winchester *et al.*¹ did not have skin abnormalities whereas those

reported by Hollister *et al.*³ had thickening, hyperpigmentation, and hirsutism. Not all cases have had corneal opacities, but these are peripheral and progressive with age. At the moment the major diagnostic criteria are the radiological features described above, in combination with at least two of the following: short stature, progressive joint contractures, corneal opacities, thickened, hyperpigmented, or hirsute skin, gum hypertrophy, and coarse facial features. Detailed histological and biochemical studies would help to subclassify these patients.

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