MORQUIO'S DISEASE

A REVIEW OF THE LITERATURE WITH A DESCRIPTION OF FOUR CASES

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Morquio's disease has been variously described as Brailsford Morquio dystrophy, chondro-osteodystrophy, atypical chondrodystrophy. In 1929 Professor L. Morquio of Montevideo described the essential features of the disease for the first time, and recognized the condition as a hereditary dystrophy of cartilage and bone resulting in dwarfism and generalized skeletal deformity (Morquio, 1929b).

Although Morquio was the first to recognize the condition as a distinct clinical entity, Brailsford (1929) also reported a case in this year stressing particularly the radiographical abnormalities. Other undoubted examples of Morquio's disease, however, had previously been described in the literature (Jaroschy, 1913; Bankart, 1912-13; Langmead, 1914-15; Wheeldon, 1920; Krabbe, 1923; Thursfield, 1925; Silfverskiöld, 1925; Grudzinski, 1928.)

Cases of Morquio's disease are still uncommonly reported and it is the purpose of this paper to present four additional cases associated with hitherto unrecorded defects. All four cases occurred in one family of eight children.

Family History

The father has not been very cooperative. The family history has been obtained from the mother who

denies any blood relationship to her husband and is possibly unaware of any. There is very strong evidence, however, that a complicated relationship does exist.

The maternal grandfather (A) married twice. Amongst his children were the mother (B) a daughter by the second wife, and the mother's half-brother (C), a son by the first wife. The father (D) is reputed to be the son of this maternal half-brother and a 'local woman' and would thus be the mother's nephew or strictly her half-nephew. This local woman married or was married

to another man who gave his name to this illegitimate child and so cloaked the relationship. Investigation of the family tree through four generations and over 50 members reveals no case of Morquio's disease other than those described below. No family history of any other deformity or mental defect has been obtained.

Father and Mother. The father is a skilled workman, industrious and intelligent, but he is disinterested in his family, who fear him. He has not been examined, but is apparently healthy. His blood Wassermann reaction is negative and his blood group is O Rh positive. He is known to have an illegitimate son or 'war orphan' abroad. This child's mother writes that he is strong and healthy, showing no dwarfing or deformities.

FIG. 1.—Eldest child at 14 years showing kypho-scoliosis with gross rotation. There is an adduction deformity of the shoulders and hips, flexion deformity of the elbows, wrists and fingers, and bilateral talipes equino-varus.

FIG. 2.—Case 1 at 11 years showing lower dorsal kyphosis. Note the standing attitude with the hips and knees flexed and the hands pressed against the thighs to give support. There is a marked knock-knee deformity.

The mother is of low intelligence and an untidy housewife. She is, however, an extremely good mother and is worshipped by her children. She seems quite content to go on having these dwarfed and deformed children on whom she bestows infinite love and care. Physical and radiological examination does not reveal any bony abnormality or other defect.

Her blood Wassermann reaction is negative and her blood group is O Rh positive, similar to that of her husband.

Unaffected Children. The second, third and sixth children appear to be physically and mentally normal.

The Eldest Child. Although not suffering from Morquio's disease this girl (Fig. 1) was mentally defective and showed microcephaly, dolichocephaly, an abnormally long palate, gross scoliosis and excessive dwarfing. She was born on May 25, 1935, and died on February 18, 1950, of intercurrent infection. She was a grossly deformed and dwarfed spastic idiot who had never walked and had been in an institute from the age of 3 years. When examined at the age of 13 she was noted to be very thin and wasted, weighing only 25 lb. Her total height was 38 in. and the head circumference only 18 in. Secondary sexual characteristics and other evidences of puberty were absent. Although there was no corneal opacity she was quite blind and the eyes had a constant jerky movement. She was unable to speak or move her limbs purposefully.

The skull presented the features of micro- and dolichocephaly. There was a relative increase in the antero-posterior diameter with a long narrow sagittal suture, which was ridged. The premaxilla was prominent and the chin recessing. The teeth, which were carious, were grossly overcrowded. The palate was prolonged posteriorly and curved down into the lower pharynx.

Other skeletal deformities included a gross scoliosis of the whole spine to such an extent that the planes of the pelvis and shoulder girdle varied by 80°. The lower limbs were spastically contracted with scissors deformity, and in addition both feet showed talipes equinovarus. Plantar reflexes could not be elicited. The upper limbs had flexion deformities of the arms, wrists and fingers bearing a superficial resemblance to the carpo-pedal spasm of tetany.

Physical examination of other systems showed no abnormal features and no enlargement of the liver or spleen. There was no radiological evidence of a generalized bony dystrophy, and the vertebrae, apart from changes secondary to disuse and spinal deformity, were normal in type.

Affected Children. These are four of the family of eight.

CASE 1. This boy (Figs. 2-5), the fourth child, was the first to present with Morquio's disease. He was born after an uneventful labour on October 6, 1939, and was breast fed. At birth the child appeared to be normal but after six weeks of life he was noticed to have a spinal deformity. He was unable to adopt a sitting posture until 18 months old and walking was delayed until the age of 4 years. From an early age, however, he 'crawled on his back' in a most unusual manner, propelling himself along in a supine position supported on the soles of his feet and the olecranons of his elbows. Speech was normal and began at 18 months.

From the age of 1½ years the child has been under clinical and radiological observation. In the early years the painless deformities of spine and limbs became progressively worse but more recently they appear to have retrogressed. In the last two years he has put on 2½ in. and 5 lb.

Apart from the chondrodystrophy he has ailed little, his worst illness being a protracted diarrhoea considered to be due to *Giardia lamblia* infestation.

General examination at the age of 11½ years revealed a happy, affectionate boy of normal intelligence showing gross skeletal deformity with dwarfism. Body measurement showed a total height of 41½ in.; height from vertex to symphysis, 21 in., and from symphysis to ground, 20½ in. His weight was 38 lb. The head, which was normal in appearance, measured 21 in. in circumference. The teeth and palate were normal. Skeletal abnormalities included a gross deformity of the spine due to a dorsi-lumbar kyphosis. There was a resultant deepening of the thorax from front to back with the formation of a prominence anteriorly at the level of the fifth costal cartilage. The neck was short and the head appeared to be pushed down into the chest. The arms were relatively long and in the erect position reached down to the knees. Fingertip to acromion measured 18 in. The olecranon processes were unusually large and

FIG. 3.—Lateral view of the spine of Case 1 at 5½ years, showing a rounded dorsi-lumbar kyphosis with anterior tongue-like projection of the tenth, eleventh and twelfth dorsal and first lumbar vertebral bodies. The eleventh dorsal vertebral body is slightly posterior to those above and below. The intervertebral space is abnormally large in the lower dorsal and lumbar regions.

FIG. 4.—Case 1 at 11 years showing flattening of the femoral capital epiphyses and ape-like shape of the pelvis.

FIG. 5.—Case 1 at 3 years showing the short, thick left humeral shaft with an irregular upper metaphyseal region and an abnormally small upper humeral epiphyseal ossific nucleus.

prevented full extension of the elbow joint. The legs measured 22½ in. only from iliac spines to heels and showed asymmetrical genu valgum. The internal femoral condyles were large and the feet were flat.

The boy stood with his legs flexed at hips and knees and would rest his hands on his thighs to help in supporting himself. The knee and hip flexion persisted on walking when he would hold his arms out behind him as a counterpoise to his body, which was thrust forward.

Crawling

Standing

Walking

The ligaments and muscles were unduly lax. Physical examination of the other systems showed no abnormality. The liver and spleen were not enlarged, there were no corneal opacities, the testes were in the inguinal canals and axillary and pubic hair had not yet appeared. Biochemical findings included a blood cholesterol level of 364 mg. per 100 ml. in 1948, which had fallen to 180 mg. in 1951. Serum calcium, inorganic phosphate and alkaline phosphatase levels were 10 mg., 4 mg. and 15 units respectively in 1948 and 11 mg., 4.8 mg. and 27 units respectively in 1951.

Radiological findings were typical of Brailsford-

Morquio chondro-osteo-dystrophy. The lateral spine showed a dorsi-lumbar kyphosis and a tongue-like projection from the anterior surfaces of D.10, 11 and 12 and L.1. The other lumbar vertebral bodies were deformed and decalcified with abnormally wide intervertebral spaces. There was no obvious anterior dislocation at the dorsi-lumbar junction but the anterior margin of the body of D.12 appeared to be at a posterior level to those of D.11 and L.1. A lower lumbar and sacral spina bifida was apparent in the anteroposterior view. There was irregularity of the acetabular roofs which sloped abnormally while the pelvis showed the ape-like shape described. There was delay in the appearance of the upper femoral capital epiphyses and in later films these were flattened. The upper ends of the femora were abnormally uniform in shape. The thorax was broad and short showing typical deformity

FIG. 6.—Case 2 at 10 years standing beside a normal boy of the same age, showing severe dorsal kyphosis and dolichocephaly. The standing attitude of flexion of the hips and knees and the support by the hands on the thighs is very pronounced. There is a marked knock-knee deformity.

secondary to the generalized kyphosis. The humeri were broad and short, the usual contours were markedly suppressed, the upper metaphyseal region was irregular and the upper epiphyses small, although not fragmented. The skull was normal in size and shape but showed early calcification of the tentorium and falx cerebri.

FIG. 7.—Antero-posterior view of the skull of Case 2 at 3 years showing dolichocephaly.

FIG. 8.—Lateral view of the skull of Case 2 at 7 years showing a beaten silver appearance and calcification of the tentorium. The sella turcica is not enlarged but appears to be deepened owing to the large posterior clinoid process.

CASE 2. This child (Figs. 6-8) is a brother of Case 1 and the fifth in the family. In addition to Morquio's disease he shows dolichocephaly, an elongated palate and mental defect.

He was born normally on June 10, 1941, and was breast fed. At birth he was noticed to have a spinal deformity and an abnormally-shaped head. The child did not sit up until he was 2 years old and walking was delayed until the sixth year. This boy also 'crawled on his back', a gait probably learnt from his brother. He did not attempt to speak until he was 6 years old.

He has been under clinical and radiological observation from the age of 2½ years. The painless deformities of spine and limbs became progressively worse in the early years, but lately appear to be stationary. In the last two years height has increased by 4½ in. and weight by 5 lb. He had not had any serious illnesses.

At the age of 9½ years he was a happy, over-affectionate child with a mental age of 4 years, gross skeletal deformity and dwarfing. Body measurement showed a total height of 42 in.; height from vertex to symphysis, of 22 in., from symphysis to ground, 20 in. He weighed 40 lb. This child's skull had a shape almost identical with that of his sister, the eldest child in the family. It showed marked dolichocephaly with a longitudinal diameter of 8 in. and a lateral diameter of only 5½ in. It showed the same long narrow, pointed ridge in the region of the sagittal suture, but it was not microcephalic as the total circumference measured 21½ in. Although the face appeared normal the hard palate was elongated and the uvula prolonged backwards.

The skeletal deformities were similar to those of Case 1, the fourth child, and need only be briefly reviewed. He showed a gross dorsi-lumbar kyphosis and a marked left dorsi-lumbar scoliosis, a short neck and a deepening of the thorax from front to back. There was partial depression of the lower sternum suggesting respiratory obstruction in childhood. The arms were relatively long and he was unable to raise them above shoulder level or fully extend them at the elbows. The legs could not be abducted beyond an angle of 45° . There was a reducible genu valgum and the feet were flat.

He would stand and walk in a manner similar to his brother and became fatigued after a walk of 100 yards. At times he would suffer from back pain of a postural type, and preferred to sit on the floor with his hands resting on the ground supporting his trunk. Although he showed less dwarfing than his brother, his deformities were more severe and widespread and he showed even more weakness of the ligaments and muscles.

The other systems showed no abnormality. The liver and spleen were not enlarged, there were no corneal opacities, the testes were in the inguinal canals and axillary and pubic hair had not yet appeared. Biochemical findings included a blood cholesterol level of 294 mg. per 100 ml. in 1948, which had fallen to 100 mg. in 1951. Serum calcium, inorganic phosphate and alkaline phosphatase levels were 10 mg., 4.3 mg. and 14.5 units respectively in 1948, and 9.3 mg., 4.9 mg. and 19 units in 1951.

Radiological findings closely resembled those of Case 1. The spine showed a dorsi-lumbar kyphosis with pointing of the anterior surfaces of L.1 and 2. The intervertebral spaces in the lumbar region were much wider than normal. The antero-posterior view showed a left dorsi-lumbar scoliosis with a spina bifida from D.11 to the sacrum and also in the cervico-dorsal region. The pelvis showed sloping irregular acetabular roofs and the ape-like shape. There was bilateral subluxation of the hip joints and flattening of the femoral capital epiphyses. The femoral necks were abnormally wide with coxa valga. The upper ends of the radius and ulna were thickened and ill-formed. The skull was dolichocephalic, the width being only 60% of the length. The pituitary fossa was normal but there was a beaten silver appearance and early calcification of the tentorium.

CASE 3. This girl (Fig. 9) was the seventh child of the family and showed the features of Morquio's disease only. She was born normally on June 30, 1946, and was breast fed. She sat up at the age of 6 months, could recognize her parents and appeared to be of average intelligence. The face and skull were normal. At birth she was noticed to have a spinal deformity which progressed to a moderate dorsi-lumbar kyphosis with a deepening of the thorax from front to back. No other features of the disease were recognized at the time of her death from 'heat stroke' at the age of $12\frac{1}{2}$ months. She was left in her pram in the sun and later found to be dead, the death being reminiscent of Brailsford's patient who died from a 'puff of wind'. Biochemical tests had never been performed on her.

Radiological changes were similar to those of the previous two cases. The spine showed a generalized

rounded kyphosis with no localized deformity. There was an anterior tongue-like projection on the eleventh and twelfth dorsal and the first lumbar vertebral bodies, and spina bifida was present in the lower lumbar region and the sacrum. The pelvis showed irregular sloping roofs to the acetabula and the femora were short and broad with wide necks. The tibiae were broad with medial beaking and small upper epiphyses which were not fragmented, while the fibulae were longer than the tibiae. The skull and pituitary fossa were normal.

CASE 4. This boy (Figs. 10-12) is the eighth and youngest child of the family. Like Case 2, he shows Morquio's disease with the addition of dolichocephaly, an abnormally long palate and mental defect. He was born by forceps delivery on May 2, 1948, and was said to have been jaundiced after birth. At birth he was noticed to have an unusually long palate and uvula which extended so far down the pharynx that the posterior end could not be seen using a spatula. The presence of nasal and oral passages could only be confirmed by passing catheters.

This defect obstructed respiration and made feeding extremely difficult. Nasal infection and snuffles were constantly present and nasal breathing was impossible. Moreover, mouth breathing was difficult and partially obstructed, causing recession of the ribs and sternum on inspiration. The first two years of life were frequently punctuated by attacks of bronchopneumonia which were treated expectantly, the child surviving only by the mother's extraordinary patience and care. Feeding was so difficult and sucking so poor that breast and bottle feeding were abandoned in favour of spoon feeding, and this was maintained with fluids alone for 20 months. When it seemed inevitable that the child would survive, the posterior third of the palate was resected at a plastic surgery unit. This was followed by an immediate improvement in breathing and feeding and no further respiratory infections have occurred.

Skull deformity was noted at birth and the spinal deformity became definite at about 6 months of age. The child's development has been retarded; although

FIG. 9.—Lateral view of spine of Case 3 at 1 year showing unusually early platyspondia. There is flattening of the vertebrae and the tongue-like projection from the anterior surfaces of the eleventh and twelfth dorsal and first lumbar vertebrae.

FIG. 10.—Case 4 at 3 years, showing lower dorsal kyphosis, chest deformity and dolichocephaly. The child was unable to stand unsupported.

he cut his first tooth at 4 months he was unable to hold up his head until he was 2 years old and at 3 years is unable to sit up. He appeared to recognize his mother at about 8 months but he only attempted his first words at 2½ years. He has been under clinical and radiological observation from the age of 2 months and the deformities have progressed.

General examination at the age of 2 years 9 months showed a happy affectionate child of retarded mentality, whose speech was limited to simple words and names. He was dwarfed and underweight and could not sit up. Weight was 22 lb. and total height 31½ in. with the length from vertex to symphysis 20 in. and from symphysis to feet 11½ in. The skull was dolichocephalic and almost identical in shape to that of the first and fifth children. The circumference was normal at 19½ in. but the longitudinal diameter was 7 in. and the lateral diameter only 4 in. There was moderate depression of the bridge of the nose and 10 upper and 10 lower teeth had appeared. The bony palate was high and elongated but the soft palate had been shortened surgically and the uvula was absent. Possibly the nasal obstruction contributed to the high palate and depressed nose.

The skeletal deformities were similar to those of Cases 1, 2 and 3, and included a marked dorsi-lumbar kyphosis and a shortening of the neck. The chest, which was asymmetrical, was flattened from side to side and deepened from front to back. It showed a vertical ridge on the right side at the costo-chondral junctions from depression of the sternum, a shape probably due to a combination of respiratory obstruction and chondro-dystrophy.

The arms were relatively short, with short fingers and trident hands. The limited movement of the shoulder and elbow joints was in marked contrast to the excessive mobility at the wrists. The legs also were relatively short but were fully or excessively mobile with unduly lax muscles and ligaments.

The liver and spleen were not enlarged and there were no corneal opacities. The Wassermann reaction was negative and his blood was Group O Rh positive. In 1951 the blood cholesterol level was 180 mg. per 100 ml., the serum calcium 9 mg., serum organic phosphate 5.4 mg. and the serum alkaline phosphatase level 26 units per 100 ml. Radiological changes were typical of chondro-osteo-dystrophy. There were wide inter-vertebral spaces in the lumbar and lower dorsal regions. Tongue-like anterior projections of the vertebral bodies were not seen in the earlier films but appeared to develop about the age of 1½ years. There was a mild degree of kyphosis centred at the dorsi-lumbar junction where there was a suggestion of anterior dislocation of D.11 on D.12; more correctly this was a lack of alignment of the

FIG. 11.—Lateral view of the spine of Case 4 at 1½ years showing pointed anterior margin of the tenth dorsal vertebral body. The intervertebral spaces in the lower dorsal and lumbar regions are very wide, and already there is an early dorsi-lumbar kyphosis.

anterior margins of D.11 and D.12 and L.1. There was a spina bifida from D.12 to the sacrum. The acetabula showed wide sloping roofs and the femora, tibiae, humeri, radii and ulnae were broader than normal. The skull was dolichocephalic and similar in shape to that of Case 2. The width was only 66% of the length and there was evidence of increased intracranial pressure.

Previously Reported Cases

Morquio (1929a and b) described two cases of familial osseous dystrophy, later (1935) adding two more cases from the same family. He established

the disease as a distinct clinical entity, recognized its hereditary nature and all its essential features. Subsequent authors have justly retained his name in their description of this disease.

Morquio recorded a family of five children, the firstborn being mentally defective and the other four children showing the typical skeletal dystrophy. The parents and the paternal grandparents were first cousins. The affected children were sexually mature, happy children of average intelligence and normal facial and cranial development. They remained apparently normal until the age of 1 year when they began to walk. From that time there developed a painless symmetrical skeletal deformity, which subsequently became arrested.

Morquio described the marked spinal kyphosis with angulation at the dorsi-lumbar region, the chest deformity with the increased antero-posterior diameter and the sternum thrust forward horizontally to a point, the raised clavicles and short neck, giving an appearance as if the head were thrust into the deformed thorax, the genu valgum from enlargement of the internal femoral condyles, the large flat feet with varus deformities, the enlargement of the head and epitrochlear of the humerus, the feeling of emptiness in the wrist joint and its excessive range of movement. Morquio stressed the lax ligaments and low muscle tone, the grating and crepitation in the joints, the difficulty in locomotion, the irregularity, deformity and delayed ossification in the epiphyses. In his earlier two cases there was a lowered serum calcium level, not present in the later cases. Other biochemical findings were normal. The pelvis and hips were not affected in his cases.

Brailsford (1931, 1935, 1948) described the radiological changes in detail. He stressed the irregularity and fragmentation of the epiphyses, the multiple centres of ossification, the large joint spaces, the short, thick long bones with coarse, irregular reticulation of the cancellous tissue and absence of regular lines in the lamellae. He described the wide flat vertebral bodies (platyspondia), some pointed in front and some wedged-shaped, the wide intervertebral discs, the erosion of the acetabula and heads of the femora, the irregularity of the carpal and tarsal bones, and the pointed bases to the metacarpals and

FIG. 12.—Case 4 at 5 months, showing thickening of the radius and ulna and irregularity of the metacarpals and phalanges, which are broad and short.

metatarsals. He attributed the prominent thorax to arrest of growth of the spine at the cervico-dorsal junction.

Since Morquio's description a number of cases have been described. The following 67 cases, reported up to the end of 1949, have been included in this analysis:—Morquio's four cases, Valentin (1930) two cases, Ruggles (1931) five cases, Dale (1931) three cases, Brailsford (1931) one case, Meyer and Brennemann (1932) one case, Brown and Macdonald (1933b) three cases, Barnett (1933) two cases, Coward and Nemir (1933) two cases, Warkany and Mitchell (1934) one case, Giraud and Bert (1934, 1935, 1936) two cases, Golding (1935) five cases, Morales Diaz (1935) two cases, Grenet and Isaac-Georges (1935) one case,

Summerfeldt and Brown (1936) two cases, Hirsch (1937) seven cases, Guérin and Lachapèle (1938) one case, Freeman (1938) one case, Marottoli and de Azcuenaga (1938a and b) one case Pohl (1939) one case, Jacobsen (1939) four cases, Crawford (1939) one case, Broekema (1940) one case, Reeves and Baylin (1941) one case, Einhorn, Moore, Ostrum and Rowntree (1941) three cases, Farrell, Maloney and Yakovlev (1942) two cases, Russo (1943) one case, Scott and Rotondo (1946) one case, Fairbank (1949) four cases and Ellman (1932, 1933, 1949) two cases. The four cases here described bring the number up to 71 cases. Doubtful cases have not been included: the father and son described by Wood and Robertson (1943) had normal spines. They may have been an incomplete form of the disease such as Hirsch (1937) describes. Sainz de los Terreros and Lacalle's case (1934) similarly may have been an incomplete form involving only the hip joints, but was more probably Legg Perthe's disease. Two of the seven cases described by Ruggles (1931), the case described by Tuthill (1934) and the two cases described by Davis and Currier (1934) were probably examples of Hurler's disease. The case shown by Cholmeley (1947) was not Morquio's disease. Other known cases were mentioned by several authors but not fully described. Brailsford (1948) mentions a further 12 cases, of varying degrees of severity, which he had personally seen. The brother and aunt of Dale's case and a sister of one of Fairbank's cases had a similar condition. The brother of Marottoli's and

de Azcuenaga's case was also affected. Jacobsen (1939) quotes an interesting family in which 20 cases occurred in five generations. He described four of these cases.

Heredity

There were 43 hereditary cases in 18 families and 23 sporadic cases. The majority of the hereditary cases occurred in siblings. Brown and Macdonald (1933a) describe a mother and daughter, and Hirsch (1937) a mother with sons and daughters affected. Einhorn *et al.* (1941) describe two first cousins who were affected. Dale (1931) mentions that an aunt of one of his cases was affected. Jacobsen (1939) described four cases in a family in which 20 members were affected in five generations. In this family the disease was transmitted as a recessive sex linked characteristic, all the cases being in males, transmission being through female carriers.

Consanguinity of parents was described five times amongst 41 families. The parents and the paternal grandparents were first cousins in Morquio's family (Morquio, 1929a). The parents were first cousins in the cases described by Golding (1935), by Farrell *et al.* (1942) and both cases of Ellman (1949). This gives an incidence of consanguinity of 12% or about 60 times that of the normal population. Brailsford (1948) mentions an additional case in which the father and mother were brother and sister. The exact relationship of the parents in the present family has not been firmly established.

Sex and Race

Male cases predominated, occurring in a proportion of six to five. Cases have occurred in most European races and in coloured peoples.

Intelligence

Morquio (1929a) stressed the fact that the intelligence was normal and many authors have supported this finding. Pohl (1939), however, maintains that where the intelligence is accurately appraised, it will probably be found to be subnormal. This has been so in the few cases in which the intelligence quotient has been stated (Pohl, 1939; Crawford, 1939; Farrell *et al.*, 1942). Others have been content to state that the intelligence was less than normal (Brown and Macdonald, 1933a; Guérin and Lachapèle, 1938; Broekema, 1940). Cases in which the intelligence has been stated to be normal, on the other hand, may have been accurately appraised without this fact being recorded. Two of our cases are mentally defective and two of average intelligence.

Face and Skull

Morquio (1929a) stated that the face and skull

were normal and this has been true in the majority of cases subsequently described.

Wide separation of the eyes with depression of the nose were noted by several authors (Broekema, 1940; Barnett, 1933; Freeman, 1938; Einhorn, 1941 *et al.*; Giraud and Bert, 1934; Fairbank, 1949).

Apparent enlargement of the head, perhaps in comparison with the dwarfing of the stature, was noted by Ruggles (1931), Dale (1931), Guérin and Lachapèle (1938) and Fairbank (1949). When this was measured in the case described by Meyer and Brennemann (1932) it was found to be normal. Actual increase in size was noted by Morales Diaz (1935), Summerfeldt and Brown (1936), Broekema (1940) and Pohl (1939).

Premature closure of the cranial sutures was unduly common in these cases. It is interesting to note that in each case it resulted in a dolichocephaly (Valentin, 1930; Barnett, 1933; Jacobsen, 1939; Einhorn *et al.*, 1941), and in two of the present series. Hydrocephalus was present in Valentin's and in Einhorn's cases. Platybasia was found in two cousins by Einhorn *et al.* (1941), and was severe enough to cause spasticity of the legs, flaccidity of the arms and loss of sphincter control. He accepts platybasia as a tenable explanation of the neuromuscular changes in Morquio's disease and relates these changes to the findings in multiple sclerosis and amyotrophic lateral sclerosis. No other author, however, mentions neuromuscular changes and it seems unlikely that platybasia is sufficient to account for the general laxity of muscles occurring in this disease. Large posterior clinoid processes were noted by Ruggles (1931), Dale (1931), Brown and Macdonald (1933a) and Russo (1943).

Other Abnormalities

Enlargement of bones in the region of the epiphyses is common (Brailsford, 1948; Fairbank, 1949), and stiffness of the joints may occur. This was sufficiently marked in Ellman's (1949) cases for rheumatoid arthritis to be diagnosed. Giraud and Bert (1934) found evidence of bilateral cervical sympathetic irritation giving a Horner's syndrome in two of their cases. Trident hands were stressed by several authors (Marottoli and de Azcuenaga, 1938a; Hirsch, 1937). Multiple fractures occurred in Crawford's case (Crawford, 1939), and a congenital short oesophagus was present in the case of Reeves and Baylin (1941). The case described by Farrell *et al.* (1942) appeared acromegalic and had hirsutes, and that described by Einhorn *et al.* (1941) had a mongoloid facies. Epilepsy was present in the brother of Crawford's (1939) case, and mental abnormality occurred in the near relatives of the cases of Morquio (1929a) and Golding (1935).

Biochemical Findings

Morquio's (1929a) first two cases had a lowered serum calcium level, 4.5 and 5 mg. %, and this was also found by Giraud and Bert (1934) 7.5 mg. %, Barnett (1933) 8 mg. %, Scott and Rotondo (1946) 8.2 mg. %. The majority of cases, however, have shown a normal serum calcium level as did Morquio's (1935) two later cases.

The serum inorganic phosphate level has been found to be normal. Other normal findings include Wassermann and tuberculin tests, blood urea, creatinine, chloride and blood count, bleeding and clotting times, serum proteins, urine and renal function tests. Freeman (1938) noted that the sugar tolerance was low and the fluid output one half of normal.

Many authors have stressed the finding of a raised basal metabolic rate and a lowered blood cholesterol level in their cases. A raised basal metabolic rate was reported by Morquio (1929a) plus 50 plus 48, by Ruggles (1931) plus 10 plus 20, by Morales Diaz (1935) plus 23, by Freeman (1938) plus 61 plus 36 plus 42, and a lowered blood cholesterol level by Freeman (1938) 142 mg. %, by Crawford (1939) 105 mg. % and by Broekema (1940) 167 mg. %.

A raised serum alkaline phosphatase level has been noted by the more recent authors (Summerfeldt and Brown, 1936, 19.2 units; Crawford, 1939, 18.8 units; Broekema, 1940, 40 units, later 15 units). It is possible that the multiple fractures accounted for the raised figure in Crawford's case (1939). It was raised at one time in all three of the cases in the present series in which it was estimated: Case 1, 15 and 27 units; Case 2, 14.5 and 19 units; Case 4, 26 units. It was normal in all three cases recorded by Einhorn *et al.* (1941) and in two cases reported by Ellman (1949). The serum alkaline phosphatase level, however, has been found to have a normal variation of 10-30 K.A. units in children (Wyatt, 1950), and it is doubtful whether any significance can be placed on the figures quoted above.

Radiological Changes

Radiological changes have been well reviewed by several authors. Brailsford (1931, 1935, 1948) and Hirsch (1937) have classified the various types of osteochondrodystrophy and the grades of Morquio's disease, thus allowing a better understanding of the whole subject. Hirsch (1937) places Morquio's disease as a generalized eccentric-osteochondroplasia, in which the epiphysis does not develop from a central nucleus of ossification but from multiple eccentric centres, thus accounting for the irregularity and fragmentation seen in the epiphyses. He asserts that the changes may not involve all the bones to the same extent and that there are cases

where only a few bones are concerned. Brailsford (1948) has classified the disease into four grades of severity; generalized and progressive, generalized but ceasing at puberty, involving the hips and spine only and that involving the hips alone. Hirsch (1937) considers that there is an associated malacia and that intermediate types between Morquio's disease and achondroplasia exist. Malacia of the hips is well shown in Ellman's (1949) cases. Osteoporosis has been stressed by several authors, but Fairbank (1949) in a recent review of the whole subject attributes this to disuse atrophy in these deformed dwarfs.

Biopsy and Necropsy

Bone biopsy was reported by Barnett (1933) to be normal. Einhorn and Rowntree (1946), however, reported irregular bone formation without evidence of osteoblastic or osteoclastic activity.

Treatment

All the methods of treatment tried have been unsuccessful in altering the natural course of this disease from an early latent stage through a florid or active stage with increasing deformity to a final stage of arrest and healing. Orthopaedic measures have been of help in preventing and correcting deformities. Calcium, vitamins A and D, pituitary and thyroid hormones have been tried.

Aetiology

Various theories have been put forward to account for this unusual disease but all appear to be inadequate. Morquio, in his earliest paper, was impressed by the finding of a lowered serum calcium level in his cases, a finding not subsequently substantiated. Ruggles (1931), Dale (1931) and Brown and Macdonald (1933a) stressed the large posterior clinoid process, presumably considering that it was evidence of a small or compressed pituitary or hypothalamus.

Platybasia (Einhorn *et al.*, 1941; Pohl, 1939), and dolichocephaly and hydrocephalus (Valentin, 1930; Pohl, 1939) have been thought to be partially or wholly responsible for the findings, and Pohl points out that an encephalogram may show actual deficiency of brain tissue. Bert (1942) considered the bony changes to be secondary to the lax ligaments and weak muscles and placed the disease as a familial mesodermal dysplasia in the same group as the syndrome of Lobstein, Oppenheim's disease and the syndrome of Danlos and Ehlers.

Several authors have suggested an endocrine basis for the disease (Brailsford, 1948; Dale, 1931; Marottoli and de Azcuenaga, 1938a; Einhorn *et al.*,

1941). Brailsford pointed out that a similar fragmentation of the epiphyses may be seen in cretins, and considered it a possibly pluriglandular endocrine disorder. Crawford (1939) suggested a relationship to Paget's disease of bone, as this disease also shows a raised alkaline phosphatase level with normal calcium and inorganic phosphate levels. Ashby, Stewart and Watkin (1937) consider that it is probably a lipoidystrophy akin to gargoylism.

Discussion

This interesting family displays two hereditary disorders; (1) Morquio's disease in the fourth, fifth, seventh and eighth children, and (2) mental defect, dolichocephaly, an abnormally long palate and possibly a scoliosis in the first, fifth and eighth children, the fifth and eighth children having both groups of abnormalities. It is interesting to speculate whether these are independent abnormalities fortuitously associated or whether they are in some way related.

There is little doubt that this chondro-osteodystrophy is of the Morquio type. Clinically the children are similar in every way to the original and subsequent descriptions of this disorder. Radiologically the vertebrae and hip joints are typical. In addition, the universal shortening of the long bones, the irregularity of the epiphyses and their late appearance would allow one to classify them with the generalized form of this disease, although there is less fragmentation than is generally found.

The second group of abnormalities is always associated in this particular family. The first, fifth and eighth children each show mental defect, dolichocephaly and an abnormally long palate, although in varying degrees of severity. None of these abnormalities occurs in other members of the family. The eldest child was an idiot, the fifth child (Case 2) when 9 years old showed a mental age of 4 years, and the eighth child (Case 4) at the age of 3 is still unable to speak and is otherwise backward. Each of these children has a dolichocephalic skull and shows the beaten silver appearance of convolutional markings. Not only is the length of the skull proportionately greater than the width, but the skulls are identical in shape, each showing the high forehead and the ridge along the sagittal suture. The eldest child was microcephalic and the most severely mentally defective. The fifth and eighth children show normal skull circumference. It seems reasonable to assume that the skull deformities have a prime influence in the development of the mental defect. Mental retardation is found frequently with dolichocephaly. (It is immaterial to the present discussion whether the dolichocephaly or the cerebral agenesis is regarded as the primary lesion.)

Each of these children showed an abnormally long palate but only in the youngest child was it sufficient to interfere with feeding and breathing. In these children the abnormality would appear to be in the hard palate, which again is probably related to the dolichocephaly, the palate also being long and narrow. It seems probable, therefore, that the mental defect and palatal deformity are secondary to the dolichocephaly.

The eldest child had a very severe scoliosis. She was a spastic idiot, unable to sit up. It is very doubtful if any effort would have been made to correct any postural defect such as scoliosis, developing as a result of her spasticity. Kyphoscoliosis was present in each of the children showing Morquio's disease, in which it is an almost invariable finding. It is therefore unlikely that scoliosis was a primary hereditary trait in this family.

It seems likely that in this family Morquio's disease and dolichocephaly are associated within one abnormal gene or group of genes. Dolichocephaly has previously been described four times in some 67 cases of Morquio's disease, an incidence of some 6%. The addition of these two cases raises the incidence to 9%. This is many times that found in the general population and strongly favours a hereditary basis for the association. Macklin (1935) considers that many hereditary traits result from the combination of several factors within one gene or group of genes in a chromosome. The factors in this family, for example, might be A, B, C, D, E, the father contributing A, B, and the mother C, D, E. The association in one child of factors A, B, C, D might cause Morquio's disease, and A, D, E, dolichocephaly. The association of all five factors would cause both diseases to be present; their dissociation, a normal child. If one accepts the consanguinity of these parents then each may carry common traits, e.g. the father A, B, C, E, and the mother B, C, D, E, making these abnormalities more common in their offspring.

Many authors are at pains to stress that this is a familial disease and not a hereditary one, because it occurs mainly in siblings. This is correct only when the terms are used in their narrowest connotation. When the hereditary factor is a dominant, it is commonly passed from parent to child. Diseases so transmitted are termed 'hereditary diseases'. When the hereditary factor is a recessive, cases occur by the chance mating of normal parents each carrying this recessive factor. Several of their children may be affected, the disease thus occurring in siblings but rarely in parent and child. Such diseases are correctly called 'hereditary diseases transmitted as recessives', but are commonly termed 'familial diseases'. Many such diseases commonly transmitted as recessives are occasionally transmitted

in certain families as dominant or even as sex-linked traits. The occurrence of Morquio's disease in a family such as Jacobsen (1939) describes serves only to emphasize its hereditary basis. The occurrence of sporadic cases of a hereditary disease transmitted as a recessive is, of course, to be expected both from the complex series of factors, which of necessity must be associated, and the smallness of the average family of to-day. Morquio's disease fulfils all the criteria of a hereditary disease commonly transmitted as a recessive.

The study of this family has, unfortunately, failed to add anything further to the aetiology, understanding or treatment of this interesting disease.

Summary

The literature of Morquio's disease is reviewed and a description of four cases in a family of eight siblings is recorded.

The parents of these children were probably related.

Dolichocephaly occurred in two of these cases and in one other child in the family. It is present in 9% of cases of Morquio's disease and is probably an associated hereditary abnormality.

Mental defect and an abnormally long palate occurred in all three children with dolichocephaly and were probably secondary to this skull abnormality.

Morquio's disease is a hereditary disease transmitted as a recessive.

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