COMMUNICATIONS
**MONGOLISM (DOWN'S SYNDROME) AND
KERATOCONUS*†**

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MONGOLISM was first described as a clinical entity and differentiated from cretinism by Langdon Down (1866). During the past few years there has been a revival of interest in the condition because of the discovery that the cells of patients with this anomaly contain an abnormal number of chromosomes. At the same time, keratoconus has been described by some European authors as one of the commoner ocular manifestations of the disease, and it has also been suggested that acute keratoconus is a not unusual complication in these patients.

Until 1956 it had always been believed that human cells contained 24 pairs of chromosomes derived equally from each parent. In that year, however, Tjio and Levan (1956) showed that our cells have only 46 chromosomes or 23 pairs, comprising one pair of sex chromosomes (the X and Y chromosomes) and 22 pairs of somatic chromosomes or autosomes. Their discovery was quickly confirmed by other workers and is now universally accepted.

In man abnormal chromosome numbers arise by non-separation of one of a pair of chromosomes in the first meiotic division. Such an occurrence involving the sex chromosomes was reported by Jacobs and Strong (1959), and has now been shown to give rise to different clinical syndromes such as gonadal dysgenesis or Turner's syndrome, where the total chromosome number is 45 (XO), and also to Klinefelter's syndrome (XXY) and the Triple X or superfemale syndrome (XXX), in both of which 47 chromosomes have been found. In these conditions the main abnormalities lie in the reproductive systems, although some of these patients are also mentally retarded.

It is also possible that non-separation of any one of the 22 pairs of autosomes could occur in man, and thus trisomy or tripling of these chromosomes of 22 varieties is within the bounds of possibility. The first autosomal trisomic syndrome described was that of mongolism by Lejeune, Gauthier,

* Received for publication January 30, 1963.

† This work was supported in part by USPHS Grant No. B2410 (C3), National Institutes of Health, Bethesda, Maryland.

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and Turpin (1959) in France and by Jacobs, Baikie, Court-Brown, and Strong (1959) in Great Britain. Both groups of investigators found that one of the smallest autosomes (No. 21) was involved, and that the total chromosome count in the mongoloid patients they examined was 47 (Figs 1 and 2).

FIG. 1.—Normal chromosomes (female).

FIG. 2.—Mongoloid chromosomes (female). Note extra member of Groups 21–22.

In man, apparently, aberrations of the autosomes lead to generalized dis-

orders of shape and size and to multiple structural abnormalities. Many of the 22 possible trisomic variations would be incompatible with life, and this is more likely the larger the size of the chromosome involved. It may be that in man the well-known fact of advanced maternal age predisposing to the birth of a mongoloid child has its effect on the chromosomes, and that with increasing age of the parent, non-separation of the particular chromosome pair is more likely to occur.

More recent work has shown that, whereas mongolism is usually the result of trisomy of a small acrocentric chromosome in Group 21-22 (Denver classification), some of these patients have an apparently normal chromosome count of 46, but, in them, the phenomenon of reciprocal translocation has occurred, and their chromosomes are therefore not all morphologically normal. In these mongoloids one chromosome of Group 13-15 is missing and, instead, there is an abnormally large unpaired chromosome which has arisen from fusion of the extra member of the 21 Group and one of the 13-15 Range.

In addition to the findings of so-called 21 trisomy in mongolism, other trisomic syndromes have now been described. In only a few of these so far have ocular abnormalities been a prominent feature. Patau, Smith, Therman, Inhorn, and Wagner (1960) described a girl with multiple congenital defects including trigger thumbs, polydactyly, capillary haemangiomata, hare lip, cleft palate, simian creases, heart defects, and mental deficiency, who also had anophthalmos. In this case trisomy of No. 15 was found. Edwards, Harnden, Cameron, Crosse, and Wolff (1960) have reported a similar child with peculiar features, low-set malformed ears, triangular mouth with receding chin, webbed neck and toes, ventricular septal defect, short fingers and toes; she was trisomic for No. 17. Some of the features of this case are suggestive of the Treacher Collins syndrome or of one of its variants. A similar syndrome with cataracts was reported by Smith, Patau, Therman, and Inhorn (1960). Atkins and Rosenthal (1961) have reported another variant of this syndrome with microphthalmos, cataract, and shallow orbits. Trisomy of an acrocentric chromosome of Groups 13-15 was found in this instance. A case with 19 trisomy has been noted among other things to have very high myopia (15-20 dioptries) in association with mental deficiency. Trisomy of No. 22 has been reported in a case of the Sturge-Weber syndrome (Hayward and Bower, 1960). On the other hand, spot chromosome checks on patients with Tay-Sachs disease, the Laurence-Moon-Biedl syndrome, arachnodactyly, and gargoylism have failed to show any abnormality.

How the chromosomal abnormality causes the defects associated with mongolism and other multiple congenital anomalies is not known. One suggestion is that it produces enzyme disturbances which could, therefore, affect many systems in the body and, in this light, it is interesting to speculate on the findings reported by O'Brien and Groshek (1962) on abnormalities of tryptophane metabolism in children with mongolism. We do know that,

in some species, this amino acid is necessary for lens metabolism and thus a link with the common finding of cataract in mongoloids is a possibility.

Our interest in mongolism arose while we were carrying out a survey of the blind and partial-sighted inmates of the Rosewood State Hospital in Maryland in 1961-62. We found a relatively large number of blind mongoloids among those examined, and keratoconus was observed in a number of these patients. It was, therefore, decided to examine all the mongoloids in Rosewood to determine the incidence of keratoconus and to see what other ocular defects were present in this group of mental defectives.

A total of 143 mongoloids was examined, representing about 6 per cent. of all the patients at Rosewood. There were 82 males and 61 females. Their ages ranged from 2 to 53 years, and 10 per cent. were Negroes, whereas the proportion of coloured patients in the whole institution was in the region of 30 per cent. Chromosome studies were being carried out simultaneously in the hospital by other investigators, and several of the mongoloids were included in this study. At the time of writing counts had been completed on four of the patients included in our survey, and all four were found to be trisomic for No. 21.

The main ocular findings in these 143 mongoloids are set out in the Table. It should be explained that the relatively low incidence of cataract in this group refers to gross lens changes, as it was not possible to examine these patients with the slit lamp, and as it was impossible to assess the refraction in most of them the incidence given for high myopia may also be too low. The universal occurrence of abnormalities of the palpebral apertures and epicanthus is explained by the fact that it was mainly on the basis of abnormal facial appearance that these patients were selected by the hospital staff for inclusion in this survey.

TABLE
INCIDENCE OF OCULAR ABNORMALITIES IN 143 MONGOLOIDS

Abnormality	Percentage
Abnormal palpebral apertures and/or epicanthus	100
Brushfield spots	38
Convergent strabismus	32
Cataract of gross degree	15
Keratoconus	5.5
High myopia (over -6 D)	5
Nystagmus	4.5
Blepharo-conjunctivitis	2
Ectropion	1.5

The occurrence of keratoconus in eight patients or in 5.5 per cent. of the mongoloids examined is a striking feature. This high figure is in accordance with that recently reported by Skeller and Öster (1951) and by Woillez and Dansaut (1960). Lowe (1948), however, in his extensive study of ocular defects in 67 mongoloids, did not record any case of keratoconus, nor did Ormond (1912) find it in a group of 42 mongoloids. Walsh (1957) mentioned that he saw one case in a 17-year-old boy, and Ford (1960) stated that "conical corneae are rare anomalies in mongolism". Rados (1948) reported two cases of bilateral keratoconus in a group of thirty mongoloids who also had cataracts.

In this series it was remarkable that only three of the eight patients with keratoconus showed the simple form of the disease. One developed the condition acutely while under our observation and four others were thought to show the end-results of such an occurrence in the past; in these patients the acute attack resulted in blindness of the affected eyes in all but one instance.

Among a second group of 160 Rosewood patients examined because of known or suspected ocular disease, keratoconus was found in only three instances, an incidence of less than 2 per cent. Again, in one patient from this control group an acute onset of the condition was observed and blindness resulted.

Acute keratoconus is a rare condition in any circumstances, and it is significant that, out of a total of 52 cases collected from the literature by Appelmans, Michiels, Nelis, and Massa (1961), seventeen examples were seen in mentally defective patients and that ten of these were mongoloids. This form of keratoconus is considered to be an acute episode in the course of the simple form of the disease; rupture of Descemet's membrane occurs and allows a sudden influx of aqueous into the cornea causing separation of the corneal lamellae and swelling and degeneration of the fibres; in addition, large cystic spaces are often formed in the substance of the cornea. The clinical picture is one of sudden cloudiness and ectasia of the cornea associated with pain, redness, and lacrimation. Acute keratoconus in mongoloids was first described by Hoffman (1956) who reported two cases. Further cases were reported by Wilde (1958) and Leffertstra (1959). Heinmüller (1959) reported a case in a mentally defective child who was probably a mongoloid, and Woillez and Dansaut (1960) saw two acute cases among five mongoloids presenting at their clinic for operative treatment for congenital cataracts. Another case was reported by Appelmans and others (1961), giving a total of eight in all. Three of these were bilateral, and the interval between the occurrence in the first and second eyes varied from 8 days to 6 months.

Through the courtesy of Dr. L. E. Zimmerman we are able to report that three examples of acute keratoconus were sent to the Armed Forces Institute of Pathology for pathological examination during the last 6 months

of 1961. Only one other similar specimen, received in 1950, was found in their files and, in this instance, a diagnosis had been made of "cyst formation in the corneal stroma". All four eyes presented a very similar gross and microscopic appearance. Three were from mongoloids aged 16, 16, and 29 years, and the fourth was from a mentally defective spastic youth aged 21. In all four cases there had been an acute onset of corneal ectasia with considerable swelling and oedema of the cornea associated with a painful, irritable eye. The eyes were removed because of "imminent rupture" or because secondary glaucoma was suspected, but the association of acute keratoconus in mongoloids was not appreciated by the clinicians at the time of enucleation. Figs 3 and 4 show examples of the gross and microscopic findings in two of these eyes.

FIG. 3.—Acute keratoconus (Gross). Armed Forces Institute of Pathology Acc. 1011522. Courtesy Dr. L. E. Zimmerman.

FIG. 4.—Acute keratoconus. Armed Forces Institute of Pathology Acc. 991726. Courtesy Dr. L. E. Zimmerman. $\times 4.3$. (Note also congenital Soemmerring's ring cataract).

In the one case observed by us during the acute phase, the picture was somewhat different. In this instance, we found no oedema or thickening of the cornea but, on the contrary, the cornea, while remaining essentially clear, became extremely thin and bulged forward in a dome-shaped fashion.

In two other mongoloid eyes an identical appearance of the corneae was noted. Again, these eyes were blind, and we suspect that a similar acute or subacute attack of keratoconus must have occurred in the past.

In a fourth case we have documentary evidence of a classical acute keratoconus in a boy who, at the age of 16, had a lamellar corneal graft performed following such an occurrence. In three of these four cases there was also evidence of associated serious ocular disease such as uveitis, cataracts, or glaucoma. In the fifth case there was evidence of past trauma to the affected eye.

Case Reports

Cases 1, 2, and 3, were three females aged 11, 23, and 43 years respectively. All showed uncomplicated, bilateral, simple keratoconus which was, as expected, more marked in the older subjects. Fig. 5 shows the right eye of the last of these patients (Case 3).

FIG. 5.—Case 3, simple keratoconus.

Case 4, a 40-year-old, moderately low-grade male mongoloid, was first seen by us in September, 1961, because of reported sudden loss of vision a few days previously. He had doubtful perception of light in each eye; the right pupil reacted sluggishly while the left pupil was inactive to light. The right cornea was clear and showed a very early degree of keratoconus. The left cornea was markedly conical, with some old scarring and vascularization. Tactile tension was normal. There were bilateral complete cataracts and right cataract extraction was, therefore, advised. While waiting for consent from the patient's relatives to have this done, an acute inflammation of the right eye developed with pain, photophobia, and lacrimation, and he was seen again by us. There was now no perception of light in either eye, the pupils were both inactive, and there was pronounced prominence of the right cornea, which was extremely thinned out, the whole cornea seeming to bulge forward in a dome-shaped fashion. There was no corneal oedema seen even with the slit-lamp, but the anterior chamber was full of inflammatory cells. No leak of lens cortex was seen and the cataracts were as previously noted. A diagnosis of acute keratoconus was made, treatment with local steroid and antibiotic drops was instituted, and a firm bandage was applied. Within 3 weeks the acute phase had subsided, the eye was quiet, and the corneal condition remained unchanged throughout a follow-up period of 9 months. In the last 3 months of this period spontaneous absorption of the

right cataract was noticed to be occurring and, when last seen, a small gap through which a faint, red reflex could be obtained was present in the centre of the lens. Visual acuity, however, remained at questionable perception of light and the pupil was still inactive.

Case 5, a 36-year-old, low-grade male mongoloid, when examined in 1940, was found to have early cataracts in both eyes. In 1959 when he was next seen the right eye was phthisical. In the left pupil some capsular remnants were seen, and it was presumed that spontaneous absorption of the cataract had occurred in this eye. He still had some useful vision in the left eye at this time. We saw him in November, 1961, and found that the left eye was also blind. The cornea showed marked keratoconus, very similar to that in the previous case. It was still clear, very thin and rather dome-shaped (Fig. 6), and we felt that an episode of acute keratoconus had taken place some time between 1959 and 1961, destroying whatever vision remained.

FIG. 6.—Case 5, acute keratoconus.

FIG. 7.—Case 7, acute keratoconus (post graft).

Case 6, a 16-year-old, low-grade female mongoloid, had had operations on both eyes for congenital cataracts in 1953, after which the left eye developed a retinal detachment, uveitis, and glaucoma, and became phthisical. The right eye was said to have been useful until recently. It was the child's mother (who visits the hospital every week) who reported that she thought that her daughter had gone blind in the second eye. When we saw the girl, the right eye was, in fact, blind with a markedly ectatic cornea which was opaque in the lower two-thirds. The eye was injected and irritable with signs of active anterior uveitis. We could not say how long this condition had been present, but we presumed that it had resulted from an acute episode of keratoconus as observed in the other cases.

Case 7, a 22-year-old male mongoloid, had a normal right eye. A lamellar corneal graft had been performed on the left eye in 1956 because of "acute keratectasia and secondary corneal infection". Since the operation the cornea had remained essentially clear, and a good visual result was obtained (Fig. 7). There is no doubt from the history in this case that the episode described in 1956 was, in fact, an attack of acute keratoconus.

Case 8, a 53-year-old low-grade female mongoloid, had a right eye which was within normal limits but the left eye was blind. The left cornea was markedly ectatic and opaque in its lower two-thirds. There was an iridodialysis in the upper outer quadrant of the iris and

the vitreous chamber was full of organized blood. Although no history of injury was available, the appearances of the eye would suggest that trauma was the cause of the blindness and also the predisposing factor in the production of the keratoconus.

Comment

It would appear from a study of the foregoing cases that keratoconus is a not uncommon ocular manifestation in mongolism. It may take the form of simple conical cornea or present as an acute episode in the course of the simple form of the disease. This episode may be triggered off by trauma, or be associated with other ocular conditions, such as uveitis, glaucoma, and cataract. The incidence of keratoconus, especially the acute form, is greater in the older age groups, our youngest patient with an acute episode being 16 years old. The acute episode may be associated with considerable swelling, clouding, and oedema of the cornea, or may appear in a more subacute form with extreme thinning, coning, or doming of the cornea; in each instance considerable loss of vision or blindness may ensue. An accurate diagnosis in the early stage may prevent unnecessary enucleation or other surgical procedures, since the acute process usually subsides spontaneously or with conservative treatment.

Summary

The finding of abnormal chromosome counts (trisomy) in patients with mongolism and other multiple congenital anomalies is discussed. The ocular defects found in a survey of 143 mongoloids in an institution for mental defectives are enumerated. Keratoconus in mongoloids is a not uncommon ocular condition, particularly in the older age groups. It may take a simple, acute, or subacute form and be associated with blindness. The literature on keratoconus in mongolism is reviewed and the clinical findings in eight mongoloid patients seen by the authors are described.

The authors would like to express their appreciation to Dr. F. B. Walsh for his encouragement in undertaking this work, and for his advice and criticism in the preparation of this paper. Our thanks are also due to the nursing staff at Rosewood for their assistance in the examination of these patients.

NOTE

Since this paper was submitted for publication a further 63 mongoloids have been examined at Gogarburn Hospital, Edinburgh. Keratoconus was present in five of these (7.9 per cent.). Again, one of the five presented with acute keratoconus and one other was blind.

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