

Corneal opacities—a diagnostic feature of the trisomy 8 mosaic syndrome

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SUMMARY An infant with trisomy 8 mosaicism had bilateral corneal opacities and multiple systemic anomalies. A review of the literature suggests that corneal opacities are a prominent feature of the syndrome and may have substantial clinical and diagnostic importance.

The normal human chromosome complement is 46, that is, 22 pairs of somatic chromosomes (autosomes) and 2 sex chromosomes. The karyotype (chromosomal constitution of the nucleus) may show an increase or decrease in the number of chromosomes, and when there is one extra autosome the condition is termed trisomy. This can arise as a result of either faulty meiosis producing a gamete with 24 chromosomes or a faulty first mitotic cleavage in the zygote. Trisomic mosaicism occurs when the chromosomal abnormality is present in only a proportion of the cells.

In trisomy 8 there is an extra chromosome 8 in every body cell, the karyotype being expressed as 47XY+8. If in addition to trisomic cells there are normal cells, the individual is termed a trisomy 8 mosaic, with a karyotype 46XY/47XY+8. Trisomy 8 mosaic individuals show sufficient clinical similarities for their condition to be designated a syndrome.¹² Fewer than 20 patients have been described with the syndrome who have ocular abnormalities.^{1–15} The findings are outlined in Table 1, and their systemic abnormalities are outlined in Table 2.

We present the ophthalmic and other anomalies present in a child with trisomy 8 mosaicism syndrome (Tr8MS), and review the reported cases of Tr8MS with ophthalmic anomalies.

Case report

The patient, a male infant, was delivered by caesarian section because of fetal distress. His birth weight was 3 kg. Both parents are Caucasian. The mother's age was 34 and the father's 37 at the time of birth. The pregnancy was uneventful apart from a urinary tract infection at 4 months. No drugs were taken.

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On the first day of life the baby developed faecal vomiting and abdominal distension and underwent a left transverse colostomy with resection of a Meckel's diverticulum. Hirschsprung's disease was thought to be the cause of his bowel obstruction, and a rectal biopsy showed aganglionosis. Radiological studies at 4 months showed multiple anomalies. There was a deformed thorax, numerous rib anomalies, broad proximal humeri, and several wider-than-normal thoracic vertebrae. The metaphyses of the humeri and femora were wide and the coccyx elongated. There was ossification of the capitulum bilaterally (this normally occurs at one year), and advanced bone maturity of the carpus with visible ossification centres. The pelvis was abnormally narrow, with dysplastic iliac bones. The femoral necks were large, and the 5th phalanges were deformed. An intravenous pyelogram was normal.

He had an unusually shaped head with prominent forehead and retrognathia, low-set large ears, and increased palmar creases, with the 'doughy' skin in the lower extremities characteristic of patients with trisomy 8 syndrome. There was a hip flexion contracture of 10° and knee contracture of 15°. Chromosomal studies were performed by Dr P. S. Gerald, of Boston, with 23 white blood cells analysed, of which 17 were of normal male karyotype, and 6 were trisomic with an extra C-group chromosome. This was found to be number 8. The proportion of cells carrying the extra 8 chromosome was 16%, establishing the diagnosis of trisomy 8 mosaicism.

At the age of 6 months the transverse colostomy was closed but 2 months later he again suffered bowel obstruction. At laparotomy he was found to have necrotising enterocolitis. This resolved after a course of parenteral feeding, drainage, and antibiotics.

By the age of 9 months he was suffering from

Table 1 *Reported ophthalmic findings in trisomy 8*

Reference	Karyotype	Findings
1	Reported in reference	(1) Squint
2	2 as being trisomy 8 mosaics	(2) L optic atrophy and small optic disc. R cataract and retrolental fibroplasia. Chronic uveitis and band keratopathy (had oxygen added in first 2 days of life)
3	46XY/47XY+8 (45% trisomic)	Strabismus
4	46XY/47XY+8 (46% trisomic)	Unilateral corneal opacity Strabismus
5	46XY+8 21-24	Cornea (L), dense nasal opacity. Slightly elevated geographic small satellite opacities, clear peripheral margin. (R) 2mm faint haze. Fundi: Tilted (R) disc, 2 streak haemorrhages (L) retina
6	47XX+8 Case (i) 47XY+8 Case (ii) Case (iii)	Exophthalmos, ptosis, androngaloid slant right eye. Telangectatic sclera (R) and (L)
8	46XX/47XX+8 Case (i) 47XX+8 Case (ii)	Normal eyes Hypertelorism Convergent strabismus Alternating squint
9	46XY/47XY+8 (23% blood) (90% fibroblasts)	Normal eyes Strabismus
10	47XY+8 Case (i) 46XY/47XY+8 Case (ii) (30% trisomy)	Esotropia Blepharophimosis, (L) microphthalmia
11	46XY/47XY+8 (50% blood, 98.5% fibroblasts)	Normal eyes Mongoloid slant Alternating convergent squint Strabismus
12		Ptosis
13		Ptosis
14		Cataract and coloboma
15	(1) (2) (3)	Heterochromia
16	(1) (2)	Heterochromia

malnutrition and malabsorption, and had a stricture of his rectal spur. Ophthalmic examination was carried out on admission to the Hospital for Sick Children, Great Ormond Street. Retinoscopy showed +4.5 D hypermetropia in both eyes. The right cornea had several dense, geographical paraxial stromal opacities. These lay superficially in the stroma and were surrounded by smaller lesions that were less opaque. Some opacities showed ghost vessels, and some were not vascularised and situated at the limbus. The left cornea had some ill-defined opacities in the paracentral and peripheral areas. The canthi were 30 mm apart. The optic discs had large physiological cups.

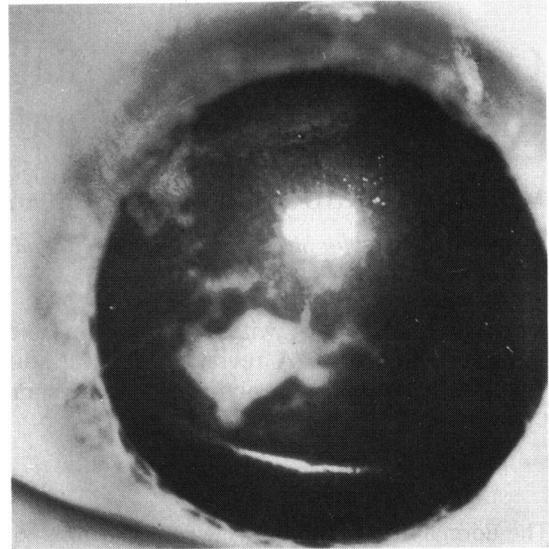


Fig. 1 *Right cornea showing geographical corneal opacities. These occupied the anterior and midstroma, and ghost blood vessels can be seen at 8 and 10 o'clock.*

At 12 months a further general examination revealed undescended testes. His knee contracture had corrected spontaneously and he had a scoliosis to the right. His weight was 8.95 kg (3rd centile) and his height was 80.5 cm (75th centile). Ocular findings were right convergent strabismus, with watering and sticky eyes.

At 18 months further rectal surgery was performed, and ocular examination, performed under the same

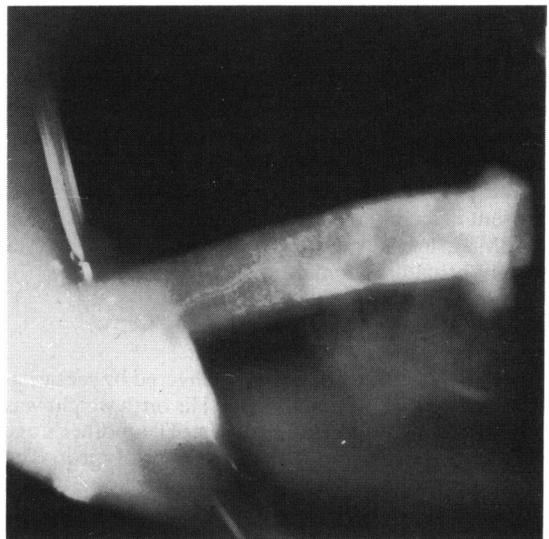


Fig. 2 *Detail of the vessel at 8 o'clock in Fig. 1.*

Table 2 Summary of clinical features of T8MS

<i>Facies</i>	<i>Skeletal system</i>	<i>Urogenital system</i>
<i>Ears</i> prominent, low set, dysplastic	<i>Trunk</i> long and slender	<i>Kidneys</i> hydronephrosis
<i>Micrognathia</i>	<i>Pelvis</i> slender	<i>Testes</i> cryptorchism
<i>Retrognathia</i>	<i>Vertebrae</i> abnormal, extra, bifid	<i>Ovaries</i> cystoma
<i>Lip</i> prominent lower lip, everted lower lip	<i>Ribs</i> extra, abnormal shapes	<i>Puberty</i> delayed
<i>Nose</i> put with flat bridge and broad base	<i>Palate</i> high arched, cleft	<i>Central nervous system</i>
<i>Head shape</i> abnormal, domed occiput, prominent forehead	<i>Joints</i> restricted articulation of shoulder	<i>Mental retardation</i> mild to moderate
	contractures — elbow	<i>Brain anomalies</i> EEG abnormal
	— hip	<i>Agnesis</i> of the corpus callosum
	<i>Syndactyly</i>	<i>Hydrocephalus</i>
	<i>Clinodactyly</i>	<i>Motor development</i> delayed
	<i>Camptodactyly</i>	<i>Speech</i> delayed
<i>Skin</i>	<i>Bone</i> thickened, shortened, tortuous, clavicles, Sprengel's deformity of scapulae, pectus excavatum, pescavo-varus	<i>Cardiovascular system</i>
<i>Dermatoglyphics</i> excess arches on fingertips.		<i>Vessels</i> anomalies
Low finger ridge count unilateral transverse palmar crease	<i>Haematology</i>	<i>Heart</i> auricular septal defect, ventricular septal defect, patent ductus, enlarged
<i>Deep skin furrows</i> of palms and soles	Reduced levels F VII	
<i>Nipples</i> widely spaced; 'doughy' skin		

anaesthetic, showed corneal diameters of 12 mm right and left, normal irides, and lenses, unchanged corneal opacities (Figs. 1 and 2), and occluded lower punctae, which were dilated and syringed to patency. Refraction was right +4.50/+0.50×90° and left +5.0 DS.

At the time of writing he is a sociable child of 20 months, whose language understanding is equivalent to an 18-month old, and whose estimated future cognitive status is not grossly delayed. He stands without support, but is unable to walk alone and cannot change from the lying position to the sitting without some aid.

Blood chemistry and growth hormone levels were within normal limits.

Discussion

Congenital corneal opacities may occur in patients either as an isolated abnormality or in association with a systemic disease or with ocular disorders. They may be inherited or acquired.

Widespread or generalised opacities occur in anterior chamber cleavage syndrome, congenital hereditary corneal dystrophy (endothelial defect), cornea plana and sclerocornea, congenital anterior staphyloma, buphthalmos, mucopolysaccharidoses and mucopolipidoses, dermoid malformation, trauma of Descemet's membrane, intrauterine or postnatal infections, and postnatal corneal exposure.

Macular or geographical opacities occur more frequently, but are seen with exposure, corneal infective ulceration, congenital macular dystrophy (recessive), ichthyosis, epidermolysis bullosa, Klinefelter's syndrome, and crystalline dystrophy.

Other cases of Tr8MS with corneal opacities have been reported. Riccardi *et al.*^{1,2} described 2 patients, one of whom had a squint and the other had optic atrophy in a small pale optic disc in one eye and a cataract and retroental fibroplasia with uveitis and keratopathy in the other. Cassidy *et al.*³ described a male child of 6 years and showed a photograph of his face which revealed a unilateral corneal opacity. The appearance was not described.

Fineman *et al.*⁴ described a female child of 1 month who had bilateral corneal opacities. One eye showed a dense, slightly elevated white geographic opacity nasally surrounded by fluffy smaller stellate opacities. There was a margin of clear cornea completely surrounding the plaque. The fellow eye had a 2 mm very faint haze.

In our patient's case the question arose as to whether the corneal opacities were a part of the syndrome or were acquired as a result of exposure keratitis during a period of obtundation that had occurred following dehydration prior to admission to this hospital. The occurrence of cases (with corneal opacities) in the literature, the characteristics of the opacities, and the absence of signs of inflammatory tissue suggest that the opacity is indeed a feature of the syndrome and may therefore be of some diagnostic significance.

The pathogenesis of the opacities and the reason for the vascularisation are impossible to ascertain, but certain possibilities arise. They may represent areas of trisomic cells or areas where, at one stage in prenatal development, there were a substantial number of trisomic cells surrounded by cells with a normal karyotype. The trisomic and normal cells have different rates of division, and some abnormal

cells may have died and caused an inflammatory focus which attracted vascularisation. This is analogous to the differential loss of the trisomic cells in Down's syndrome mosaicism,^{17,18} resulting in the decrease in the proportion of abnormal karyotypes to normal karyotypes. However, corneal opacity in apparently complete trisomy 8 has not been reported, but the number of cases is small.

It is possible that there was a prenatal or perinatal corneal infection (involving both eyes), but there was no evidence of this from the history, and it is perhaps unlikely that the resulting opacity would be macular and not diffuse, and its occurrence in other cases is very suggestive of a prenatal determination.

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