Syndrome of the month

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The oculocerebrocutaneous (Delleman) syndrome

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In 1981 Delleman and Oorthuys¹ reported two children with congenital malformations consisting of orbital cysts, cerebral malformations, focal dermal defects, and skin appendages. They suggested the term 'oculocerebrocutaneous' syndrome to describe this group of malformations. Three other cases have subsequently been reported.²⁻⁴

We review the features in these five published cases together with four previously unreported cases and discuss the features which distinguish it from other disorders with similar manifestations.

Clinical features (table 1)

OCULAR

The striking ocular feature seen in eight of nine of

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TABLE 1 Features of the oculocerebrocutaneous syndrome.

Feature	Case								
	1 ¹	2 ¹	3 ²	4 ³	5 ⁴	6	7	8	9
General									
Sex	M	M	F	M	F	F	M	M	M
Developmental delay/mental retardation	+	+	+	+	-	-	+	+	+
Convulsions	+	+	+	+	+	-	+	-	+
Generalised asymmetry	+	+	+	-	-	-	-	-	-
Cleft lip/palate	-	-	+	-	-	-	+	+	-
Ocular									
Orbital cyst*	B	R	B	L	R	B	R	R	-
Microphthalmia	+	+	+	+	-	+	-	-	+
Eyelid coloboma	+	+	+	-	-	-	-	-	+
Hamartoma	+	-	-	-	+	-	-	-	-
Coloboma of lateral canthal region	-	-	-	-	-	-	-	-	+
Skin									
Periorbital appendages	+	+	+	+	(+) (post-auricular)	+	+	-	+
Hypo/aplasia	+	+	+	+	+	+	+	+	+
Punch-like defect	+	+	+	+	+	-	+	+	-
Skeletal									
Skull defect	+	+	+	+	-	-	?	-	+
Rib dysplasia	-	+	+	-	+	+	-	-	-
Vertebral anomalies	?	+	-	-	-	-	?	-	-
CT scan									
Intracranial cysts	+	+	?	+	+	+	-	+	-
Agensis of the corpus callosum	+	+	?	-	+	+	-	-	-

*B=bilateral; R=unilateral, right; L=unilateral, left.

FIG 1 Orbital cyst of right eye in case 8.

the cases is an orbital cyst (fig 1), which was bilateral in three cases. The histology of the cyst in case 4 showed it to be a neuroepithelial hamartomatous structure with the solid portion containing primitive glial, retinal, and medullary tissue along with lenticular and capsular remnants, distorted choroidal material, and bundles of striated muscle. In the solid portion of the cyst the retinal neuroepithelium had formed dysplastic rosettes. The bulk of the cyst wall consisted mostly of primitive neuroepithelium that resembled brain tissue, with areas lined by medullary and pigmentary epithe-

FIG 2 Area of hypoplastic skin above left ear in case 6.

FIG 3 'Punch-like' defect lateral to right angle of the mouth and periorbital skin appendages in case 7.

lium. In the one other case in which histology of the orbital cyst was available (case 1), that on the right was described as a hamartoma and that on the left consisted of ectopic brain tissue.

Other distinctive ocular anomalies include microphthalmia, which was present in five cases, and eyelid colobomata in four cases. Case 9 differed from the others in not having an orbital cyst but a coloboma of the lateral canthal region and bilateral subconjunctival dermoids.

SKIN

Areas of aplastic/hypoplastic skin are a prominent feature, having been observed in all cases (fig 2). There does not appear to be a particular pattern of distribution of skin involvement, although in five cases one or two areas of aplastic/hypoplastic skin were present above one or both ears. In seven cases a further unusual 'punch-like' defect of the skin was present (fig 3). Histology of one of these 'punch-like' defects in the one case available showed focal inflammatory changes.

Eight of the nine cases had skin appendages (fig 4). These were primarily present in the periorbital region in seven cases and in the postauricular region in one. Histology of an appendage in one case showed normal epithelial structure. This is in marked contrast to the characteristic histology seen in the skin in the Goltz syndrome in which fat cells replace connective tissue in the corium.

FIG 4 Skin appendages in the periorbital region on both sides in case 6.

CENTRAL NERVOUS SYSTEM

A characteristic CT scan finding consisting of either multiple intracranial cysts or agenesis of the corpus callosum was found in six cases (figs 5 and 6). Four cases had both findings while two others had multiple intracranial cysts only. In three cases (5, 6, and 8) the cyst was situated in the posterior fossa

and was associated with cerebellar dysplasia in two cases (5 and 6) and a Dandy-Walker malformation in the other case (8). The intracerebral cyst was located solely in the cerebral hemisphere in case 4 and extended both supra- and infratentorially in case 1. In addition, in case 5 there was ectopic grey matter present throughout the entire right cerebral hemisphere.

Case 9 differed in not having the typical CT findings of agenesis of the corpus callosum or intracranial cysts, but did have cerebellar hypoplasia, hydrocephalus, and unilateral 'cerebral atrophy'.

Follow up CT scans were performed in three cases (1, 4, and 8). This showed the appearance of multiple porencephalic cysts in case 4, obstructive hydrocephalus owing to a large occipital cystic tumour in case 1, and an increase in lateral ventricular size in case 8 which was treated by ventriculoatrial shunting.

A contrast enhanced CSF study was performed in case 8 showing CSF entering the optic canals bilaterally with slow communication of fluid from the spinal subarachnoid space to the posterior fossa cyst and into the ventricular system.

SKELETAL

Minor skull defects were noted in five cases. In two of the three cases reported by Delleman,^{1,2} these consisted in one instance of a underdeveloped right orbit owing to absence of the zygomatic process as well as the sphenoid part of the lateral wall, and in the second of an occipital meningoencephalocele.

FIG 5 CT scan of the brain in case 6 showing agenesis of the corpus callosum as seen by the bodies of the lateral ventricles failing to come together in the midline. In addition they are separated by a small cyst.

Specific details of the third case were not included. The case reported by Ferguson *et al*³ had wide sutures with calvarial thinning. The skull involvement in case 9 consisted of wide cranial sutures.

Rib dysplasia was also found in four cases (fig 7). Three cases had generalised asymmetry and one had a thoracic scoliosis of the spine.

GENERAL

Three cases had cleft palate of an unusual type, described as an aplastic right hemipalate in case 7 and in case 8 as an incomplete right soft palate. The cleft palate in case 3 was associated with mild micrognathia.

In addition, case 2 reported by Delleman had undescended testes with an underdeveloped scrotum.

Natural history

Psychomotor developmental delay is a prominent feature. Seven of the nine cases had significant

FIG 6 CT scan of the brain in case 6 showing large cystic space of CSF density occupying the cerebellar hemisphere area extending to the fourth ventricle, as well as a cystic space anterior to the brain stem. The orbital appearances are grossly abnormal with cystic structures on both sides, with the globes represented by microphthalmic remnants.

FIG 7 Chest x ray of case 6 showing widening of the diameter of the anterior end of the left fourth rib and posterior end of the left ninth and tenth ribs.

developmental delay with convulsions. Two cases (4 and 6) appeared to be developing normally although in both instances the period of follow up was limited (seven months and four months respectively).

One patient (case 1) died at the age of two years as a result of obstructive hydrocephalus. Two others developed hydrocephalus which was successfully treated by shunting. Early recognition of the possible central nervous system involvement and complications might improve the apparently poor outcome, although in case 8 CSF shunting did not alter intellectual development.

Differential diagnosis

The Goltz and Goldenhar syndromes have similar ocular and dermatological features⁵ but there are many features which allow one to differentiate between them (table 2). Some of the eye and skin features suggest the possibility of the dominant syndrome reported by Lee *et al*⁶ and Hall *et al*,⁷ which consists of haemangiomatous branchial clefts, lip pseudoclefts, and an unusual facial appearance.

Aetiology, genetics, and embryology

The origin of the features in this disorder is unclear.

TABLE 2 Features of disorders in differential diagnosis of the oculocerebrocutaneous syndrome.

Features	Syndrome			
	Delleman	Goldenhar	Goltz	Lee et al, ⁶ Hall et al ⁷
<i>General</i>				
M:F	6:3	1:1	1:10	3:2
<i>CNS</i>				
Mental retardation/developmental delay	+	+/-	+/-	-
Multiple intracranial cysts	+	-	-	?
Agenesis of the corpus callosum	+	-	-	?
<i>Skin</i>				
<i>Appendages</i>				
	Peri-orbital	Pre-auricular	Peri-oral/anal	-
Hypo/aplasia	+	-	+	+
Punch-like defects	+	-	-	-
<i>Ocular</i>				
Orbital cyst	+	+/-	-	+/-
Microphthalmia	+	+	+	+
Eyelid coloboma	+/-	+	-	(Iris/retina)
Epibulbar dermoid	-/+	+	-	-
<i>Skeletal</i>				
Skull defect	+	+	-	?
Rib dysplasia	+	+	+	?
Vertebral anomalies	+/-	+	+	?
Hand/foot anomalies	-	+	+	+
Generalised asymmetry	+/-	+	+	-
Facial asymmetry	+/-	+	+/-	-

Chromosome analysis was normal in eight out of the nine cases where this was performed. Enquiry into the family history in case 1 showed a paternal grandmother with unilateral anophthalmia, and in case 8 there was bilateral coloboma in the mother and an eye cyst in a paternal first cousin. In addition, the parents of cases 2 and 7 had had two spontaneous abortions.

It is possible that the condition could be the result of an autosomal dominant gene with reduced penetrance and variable expression and that the majority of the cases represent new mutations, given the above findings. Autosomal recessive inheritance cannot be ruled out, although consanguinity has not been reported and there have been no reports of recurrences within sibships. Approximately equal numbers of both sexes are affected (M:F 6:3) making X linked inheritance unlikely.

Although recurrences have not occurred in any of the families reported, prenatal diagnosis should be possible by detection of the intracerebral cysts using prenatal ultrasound studies. It is not known, however, at what stage in pregnancy these appear in order to predict how reliable these findings might be.

Cystic eye defects arise from defective closure of the embryonic fissure at the fourth to fifth embryonic

week. The embryonic fissure forms during the invagination of the optic vesicle and optic stalk at the 5 to 8 mm stage (five to six weeks) of gestation. The fissure allows the hyaloid vascular system to enter the future vitreous cavity and the sprouting nerve fibres to grow from the retina to the lateral geniculate body. The embryonic fissure begins to close centrally around the 8 mm stage (six weeks) and fuses both posteriorly and anteriorly by the 20 mm (seven to eight weeks) stage. Improper fusion of the lips of the fissure may produce a defect in the neuroectodermal and uveal tissue, manifesting as a typical coloboma consisting of a layer of sclera lined by a thin membrane of maldeveloped ectoderm. Proliferation of the neuroectoderm at the lips of the persistent embryonic fissure may form a cyst, the cavity of which is continuous with the space between the two layers of the optic cup.^{8 9}

Skin tags arise as a result of disturbance along the line of coalescence of the facial buds during the fifth to sixth embryonic week.¹⁰ Ferguson *et al*³ suggested that the collection of features seen in these patients is part of a spectrum of associated defects which could be induced by factors which interfere with morphogenesis in the fifth to sixth week of gestation. Happle¹¹ has recently proposed that this syndrome, like a number of other sporadically

occurring disorders with an irregular distribution of skin involvement, may be the result of the action of an autosomal 'dominant' lethal gene which is only compatible with survival in the mosaic state. The possibility of a submicroscopic deletion being responsible cannot be ruled out at present.

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