Eyes in arhinencephalic syndromes

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The term arhinencephaly was coined by Geoffrey-Saint-Hilaire in 1882 (cited by Morton, 1947) when describing a 'monster' without a properly developed nasal region. He made no reference to the actual rhinencephalon. Kunderat (1882) embraced the rhinencephalon in his study and subsequently the term has come to refer more to brain abnormalities than the nose alone. Yakovlev (1959) found that the rhinencephalon is never completely absent, and De Myer (1971) suggested that the term arhinencephaly should be restricted to simple absence of the olfactory bulbs and tracts, without the often gross associated defects of the brain (the holoprosencephalies).

In this series absence of the first cranial nerve has been taken as the common denominator in the arhinencephalic syndromes. Although De Myer and Zeman (1963) showed that this abnormality may not be present in the holoprosencephalic spectrum of abnormalities, this is very uncommon and has not been found in this study.

Clinical material

Necropsy examinations have been carried out on 22 infants with arhinencephaly at this and associated hospitals over a 15-year period. KML was alerted to arhinencephaly in his first case by the inclusion of this abnormality in one of severe multiple malformations. Thereafter arhinencephaly, even of the *forme fruste* variety where there is only hypoplasia of the olfactory bulb and absence of the olfactory tract and trigone without other obvious brain abnormality, was actively sought in all necropsy examinations. Therefore selection of cases with such features has not occurred. However, isolated 'absence' of the first cranial nerve has not been observed in the 1735 consecutive autopsies (Laurence, 1975) and this is also a rare occurrence in the literature (Stewart, 1939). Furthermore, the incidence of associated chromosomal abnormalities is not higher in this series than previously reported (Aita, 1969).

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FIG. 1 Case 1. Microcephalic infant with severely abnormal facies

FIG. 2 Low power photomicrograph of eye of Case 1 showing micropthalmia, macrolentis, and posterior cyclopic tendency with deficiency in sclera (arrowed) through which tissue surrounding choroid protrudes. Optic nerve (N) is included in section. Haematoxylin and eosin. $\times 5$

FIG. 3 Case 1. Macrolentis (L) in situ filling globe. $\times 5$

Results

The clinical features, necropsy, ophthalmological, and cytogenetic findings are given in the Table. Apart from the extreme macrolentis in Case 1

(Figs 1, 2, and 3), the posterior fusion of the eyes (Case 3) and the skin-covered limbal lipoma (Case 8), all the ocular findings have been previously described in arhinencephalic syndromes. Probably all the ocular findings that have been described in

Table *Features of arhinencephalic patients*

<i>Case number</i>	<i>Survival</i>	<i>Sex</i>	<i>Gestational length (weeks)</i>	<i>Birth weight (g)</i>	<i>Principal external features</i>	<i>Principal internal findings</i>	<i>Ophthalmological features</i>	<i>Cytogenetics findings</i>
1	2 weeks	F	42	1820	Severe microcephaly Low set ears (Fig. 1) Incomplete separation of anus and vulva Low insertion of thumbs Single palmar crease Congenital dislocation of hips	Heart malformation with atrial septal defect patent ductus arteriosus left superior vena cava draining into right atrium Choanal atresia Bifid uvula Hypoplastic kidneys Alobar holoprosencephaly with vestigial olfactory tracts	Hypertelorism (Fig. 1) Severe micropthalmia (8.5 mm and 9.5 mm antero-posterior) Abnormal and deficient retina Posterior 'cyclopic tendency' abnormality (Fig. 2) Gross macrolentis (Fig. 3) Hypoplastic optic chiasm, optic nerve (1.0 mm diameter),* and optic disc	Normal female (46 XX)
2	Still-born	F	35	2100	Large abnormal head (Fig. 4) 1 cm long proboscis Short arms with an ulnar supernumerary digit on each side Short legs Bilateral congenital dislocation of hip	Bifid epiglottis Hypoplastic lungs Malrotation of intestines and universal mesentery Absent pituitary Absent fetal zone in adrenals Brain with alobar holoprosencephaly Absent olfactory tract and second and third nerves Hydrocephalus Hypoplasia of cerebellum	Anophthalmia Absent optic nerves Absent optic foramina Absent sella turcica (Fig. 5)	Normal female (46 XX)
3	5 min	F	36	2000	2 cm long proboscis (Fig. 6) Low set ears Rocker bottom feet	Multi-lobulated kidneys Alobar holoprosencephaly with absent olfactory tracts Ethmocephaly	Severe hypotelorism (Fig. 6) Severe micropthalmia (antero-posterior 11 mm) with posterior fusion of eyeballs (Figs 7 and 8) Optic nerve hypoplasia (1.7 mm diameter)* Hypoplastic chiasm	Trisomic female (47 XX, D+)
4	1 hr	M	33	1480	Microcephaly Deficiency of scalp Midline hare lip and hypoplasia of nose Low set ears Micrognathos Poorly developed penis Single palmar creases Rocker bottom feet with six toes each	Cleft palate Malrotated intestine and universal mesentery Large dysgenetic kidneys with microcysts Brain with alobar holoprosencephaly and semi-vestigial olfactory tract Large suprarenals with cytomegaly	Hypotelorism Mongoloid slant of palpebral apertures Microphthalmia (13 mm antero-posterior) Colobomata of irides, ciliary bodies, and lenses Abnormal retinal folds Optic nerve diameter 2.9 mm*	Trisomic male (47 XY, D+)
5	20 min	M	38	2100	Bilateral hare lip with floating premaxilla Micrognathos Low set ears Webbing of neck Single palmar creases Hypoplastic penis	Cleft palate Patent ductus arteriosus Tracheo-oesophageal fistula and oesophageal atresia Meckel's diverticulum Polycystic kidneys Brain with absent olfactory tracts and vestigial olfactory bulbs	Eyes normal size (16.5 mm antero-posterior) Hypoplasia optic nerve (1.6 mm diameter)* colobomata and hypoplasia of optic discs	Trisomic male (47 XY, D+)

Case number	Survival	Sex	Gestational length (weeks)	Birth weight (g)	Principal external features	Principal internal findings	Ophthalmological features	Cytogenetics findings
6	72 hr	M	38	2670	Micrognathos (Fig. 9) Low set ears Extra ulnar digit (right) (Fig. 10) Single palmar crease Hypoplastic penis Sacrococcygeal pit Rocker bottom feet	Patent ductus arteriosus Cleft of soft palate Meckel's diverticulum and malformation of gut Polycystic kidneys with hydronephrosis Double ureter right side Vestigial olfactory tracts in the otherwise normal brain	Prominent epicanthic folds Antimongoloid slope of palpebral fissures Eyeballs 14 and 16 mm (antero-posterior) Colobomata of irides and ciliary bodies Mass of retrolental white tissues (Fig. 11) Abnormal retinal folds (Fig. 12) Absence of retinal vessels Aplasia of optic disc Optic nerve 1.8 mm × 0.9 mm* Chiasm normal	Fibroblast cultures failed
7	45 min	M	37	2500	Bilateral hare lip with hypoplastic premaxilla Micrognathos Low set abnormal ears Small exomphalos Hypoplastic penis Flexion deformity of wrists Rocker bottom feet	Cleft palate Malformed heart with ventricular septal defect and patent ductus arteriosus Absent left umbilical artery Polycystic kidneys Double ureter Large suprarenal gland Brain with absent olfactory tracts and vestigial olfactory bulbs	Mongoloid slant to palpebral fissures Microphthalmia (11 mm antero-posterior) Colobomata of irides and ciliary bodies Mass of white tissue behind lens continuous with infolding of sclera over ciliary colobomatous area (Fig. 13) Optic nerve diameter 2 mm × 1.3 mm	Trisomic male (47 XY, D+)
8	72 hr	F	40	3400	Microcephaly Median hare lip Flat nose Micrognathos Grossly abnormal low set ears with accessory auricles Rocker bottom feet	Cleft palate Malformed heart with atrial septal defect, large intra-ventricular septal defect, transposition of great vessels and stenosis of mitral valve Semi-lobular holoprosencephaly with vestigial olfactory tracts and absent cerebellum	Mongoloid slant to palpebral fissures Eyes normal size (20 mm antero-posterior) 1 cm diameter skin-covered lipoma in right palpebral fissure (Figs 15 and 16) Colobomata of optic nerve heads (Fig. 17) Optic nerve diameter 2.1 × 0.8 mm*	Cultures failed

* (i) mean cross-sectional dimensions of the optic nerve near the chiasma in 24 normal neonates of over 32 weeks' gestation was 1.8 × 2.7 mm (range 1.25 – 2.0 × 1.9 – 3.5 mm)

(ii) mean diameter of the optic nerve just before entry into the eyeball in six normal neonates of over 32 weeks' gestation was 2.6 mm (range 2.2 – 3.1 mm)

the trisomy D syndrome can occur in the arhinencephalic cases with trisomy D.

In all eight cases clinically ascertainable ocular physical signs were present. These varied from anophthalmia (Case 2, Figs 4 and 5) to normal-sized eyes with isolated colobomata of optic discs (Case 8) or hypoplasia of the discs (Case 5). Ethmocephaly (absence of the ethmoid bones) was present in Case 3 (Figs 6 and 7) and this allowed posterior fusion of the globes. This represents a *forme fruste* of the cyclopean process. Extreme hypotelorism may represent the clinical counterpart, but Case 1

shows that hypertelorism can occur with the cyclopic tendency.

Discussion

Cyclopia was not present in this series. It is the most dramatic ocular abnormality in arhinencephaly and has received the most attention in ophthalmic literature. It is, however, a rare condition invariably associated with the gross brain abnormality of alobar holoprosencephaly, and incompatible with life. Many of the cyclopean eyes reported are fused

FIG. 4 *Facies of Case 2 showing large head with anophthalmia and proboscis*

FIG. 6 *Facies of Case 3 showing proboscis and hypotelorism. Microphthalmic eyes showing posterior fusion were found inside the orbits*

FIG. 7 *Dissection of eyes, Case 3, showing posterior fusion (arrowed)*

FIG. 5 (right) *Base of skull of Case 3 showing the absence of optic foramina and pituitary fossa. Site normally occupied by fossa is arrowed*

FIG. 8 Low power photomicrograph of communication between two eyes showing both abnormal choroidal and retinal elements. Communication (C) and abnormal eyeballs (E) are labelled. Haematoxylin and eosin. $\times 5$

eyes with duplication of various ocular components—for example, Case 2 (Gartner, 1947).

In many cases the facial abnormalities predict the state of the brain (De Myer, 1971), but this is not invariable (Fischer, 1905, cited by Morton, 1947; Snodgrass, Butler, France, Crome, and Russell, 1966; Bligh and Laurence, 1967; Hintz, Menking, and Sotos, 1968; Robain and Gorce, 1972).

The severity of eye involvement in this series is parallel to the severity of brain involvement in Cases 1 to 5 but not in Cases 6 to 8 (Figs 9–17). Prediction of the brain from the eyes is not possible, therefore, but the changes found in the eyes in this series should arouse the ophthalmologists' interest in the brain and the endocrine system (see below). This is especially so when such ocular abnormalities are associated with hypotelorism (suggesting a tendency to cyclopia), and external nasal abnormality (suggesting arhinencephaly), or cleft lip/palate (Kundrat, 1882; De Myer, Zeman, and Palmer, 1964).

Recognition of treatable endocrine abnormalities in the more extreme cases of arhinencephaly is not important. Such endocrine abnormalities are consequent to maldevelopment of the pituitary-hypothalamic axis and have been found at necropsy for many years. Klopstock (1921) claimed absent adrenal glands in a cyclopic patient, and Haworth, Medovy, and Lewis (1961) in two out of three arhinencephalic cases, failed to find the pituitary gland and the adrenals were hypoplastic. Case 2 (see Fig. 5) shows an absent pituitary gland.

Badtke (1948) found an enlarged adrenal gland in an arhinencephalic infant and Cases 4 and 7 also showed this.

Pituitary malfunction has also been recognized clinically. Pitressin responsive diabetes insipidus, adrenal insufficiency (Hintz and others, 1968), and

diabetes insipidus (Robain and Gorce, 1972) have been described. Ladurner, Summer, and Reinisch (1972) describe the clinical and pathological features of a two-year-old anophthalmic arhinencephalic with pituitary dysfunction. The similarity of this report to Case 2 in this series is striking.

Recognition of such endocrine dysgenesis becomes important in the less severe cases of arhinencephaly which may survive to adult life, especially in view of the report of isolated endocrine dysgenesis (growth hormone deficiency) in a sibling of two familial cases of holoprosencephaly (Romshe and Sotos, 1973). This finding shows that in the familial cases of arhinencephaly the severity of clinical involvement can vary from neonatal death to isolated, treatable pituitary dysfunction.

The possibility also exists that arhinencephaly can occur with hypothyroidism as McDermott, Insley, Barton, Rowe, Edward, and Cameron (1968) described both conditions occurring in syndromes caused by deficiency of the short arm of chromosome 18.

The familial nature of some cases of arhinencephaly has been noted for many years (Klopstock, 1921; Grebe, 1944). These familial cases showed great phenotypic variability, involving many systems. That a prezygote, preuterine origin of arhinencephaly can occur is suggested by the rare occurrence of twin cyclopean or cebocephalic monsters (Ellis, 1865; Duyse, 1905). Morton (1947), on the basis of detailed anatomical dissection and correlation with embryology, favoured a genetic origin of his case of arhinencephaly. Gruber (1948) also argues for a genetic origin because of the association of typically hereditary malformations with cyclopia and the high incidence of abortions in the families involved.

Cyclopia has been produced experimentally in

FIG. 9 Head of Case 6 showing low set ears and micrognathos

fish (Stockard, 1909; Majina and Ingalls, 1966), and induced in sheep by ingestion of the plant *Veratrum californicum* (Babbott, Binns, and Ingalls, 1962). Rarely, in man has a relationship between arhinencephaly and maternal diabetes been described (Dekaban and Magee, 1958; Robain and Gorce, 1972, Case 9), or simulation of arhinencephaly by toxoplasmosis (Liebaldt, 1972).

Despite these findings, it is becoming increasingly recognized that chromosomal abnormalities may underly cyclopia and other arhinencephalic syndromes in man. Arhinencephaly has recently come into prominence because of its common occurrence in the trisomy D syndromes (McKusick, 1961; Miller, Piccard, Alkan, Warner, and Gerald, 1963; Laurence, 1966). Conversely, about 40 per cent of arhinencephalics have trisomy D (Laurence, 1966; Aita, 1969). It has been suggested that when there are few other congenital abnormalities, arhinencephalics have normal chromosomes (McDermott and others, 1968; De Myer, Zeman, and Palmer, 1963). Normal chromosomes with multiple congenital abnormalities have been found in Cases 1 and 2 and these have also been found by others (Miller and Seldon, 1967; Landau, Barry, and Koch, 1963;

FIG. 10 Left hand of Case 6 showing transverse palmar crease and ulnar polydactyly

FIG. 11 Section of eyeball of Case 6 showing uveal coloboma (Co) which is continuous with mass of retrolental tissue (T). Abnormal retinal folds are seen radiating to this. Cornea (C) and iris (I) are also labelled. $\times 4$

Robain and Gorce, 1972). As Miller and Seldon stated, however, 'it is important to acknowledge that in these apparently non-trisomic patients such chromosomal material may still be present attached to another chromosome in an amount too small to be detected by current methods of study'. Moreover, other cryptogenic chromosomal defects cannot be excluded, especially as deletion of the short arm of

FIG. 12 Abnormal retinal folds, Case 6 Haematoxylin and eosin. $\times 60$

FIG. 13 Dissection of eye of Case 7 to show iris (I), coloboma (Co), ingrowth of sclera (IS) at colobomatous site. Cut edge of sclera (S) is indicated and also underlying ciliary body and choroid (CH). $\times 6$

chromosome 18 has been missed in cebocephaly (Haworth and others, 1961, Case 1), and diagnosed retrospectively (Uchida, McRae, Wang, and Ray, 1965, Case 3). Gorlin, Yunis, and Anderson (1968) found deletion of the short arm of chromosomes 18 in cebocephaly with little other congenital abnormality. Other arhinencephalic syndromes with deficiency of the short arm of chromosome 18 have been described by Faint and Lewis (1964-cyclops); Nitowsky, Sundhvananda, Konigsberg, and Weinber (1966-cyclops); Pfeiffer (1966); McDermott and others (1968). Arhinencephaly has also been described with trisomy E (17-18 group) by Robain and Gorce (1972, Case 13) and France (quoted by McDermott and others, 1968).

The mosaicism of an extra piece of chromosome material in a cyclops (Pfitzer and Muntefering, 1968) is similar to the cytogenetic finding in the oculo-anal syndrome (Schachenmann, Schmid, Fraccaro, Mannini, Tiepolo, Perona, and Sartori, 1965).

France (see McDermott and others, 1968) found a deletion of chromosome 5 and Cohen (1966) described cyclopia occurring with a normal

FIG. 14 *Photomicrograph of Case 7. Retrolental mass, consisting largely of abnormal retinal elements. Haematoxylin and eosin. $\times 100$*

monosomy G mosaicism. These seem to be the only reports in which the chromosome abnormalities were definitely not involving the D (13-15) or E (17-18) groups of chromosomes. Trisomies of these groups are now well recognized causes of ocular abnormalities and it would seem deletions, partial trisomies, and mosaicisms cause similar developmental defects, as seen in the arhinencephalic syndromes.

In familial cases of arhinencephaly with normal chromosomes De Myer and others (1963) suggested a recessive inheritance, but familial cryptogenic chromosomal abnormality has to be considered also. Thus Hintz and others (1968) described familial holoprosencephaly with normal chromosomes, but the facial cleft, single transverse palmar creases, familial polydactyly, and recurrent abortions suggest that such a cryptogenic chromosomal defect is present.

Overt familial chromosomal defects in familial arhinencephalic syndromes have been described by Uchida and others (1965), McDermott and others (1968)—short arm deficiency of chromosome 18. Conen, Erkman, and Metaxotou (1966) found presumptive familial trisomy D in holoprosencephaly (Case 1), whilst Pfitzer and Müntefering (1968) described a carrier state of chromosomal abnormality in four related mothers, where in addition to 11 congenitally defective births and abortions four cyclops were born.

FIG. 15 *Facies of Case 8 showing grossly abnormal ear, dermal lipoma, and grossly abnormal nose*

FIG. 16 Low-power photomicrograph through eyeball and lipoma, Case 8. Haematoxylin and eosin. $\times 7$

It is probable that many of the reported twin and familial arhinencephalics previously reported had abnormal chromosomes. It is important to recognize these syndromes clinically and ophthalmologically, and to determine their relationship to such chromosomal abnormalities. The recognition of carrier states, and the *in utero* cytogenetic studies of amniotic cells may spare the unfortunate parents of such monstrosities from similar traumatic experiences.

Summary

The ocular features of eight cases of arhinencephaly

have been described. Prediction of the degree of brain involvement from the eye defects could not be made, but eye abnormalities were present in all cases. The relationship of these syndromes to chromosomal abnormalities is emphasized. In the less severe cases treatable endocrine dysgenesis must be excluded.

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FIG. 17 *Coloboma of optic nerve head, Case 8. × 20*

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