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Variable expressivity of hypertelorism in three siblings with Greig syndrome

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Two sisters and one brother are reported with a complex of congenital malformations, hypertelorism, mental retardation, flattened nasal root, divergent strabism, mongoloid palpebral fissures, malformations of the ears, pathologic alterations of the eye-fundus in terms of optic nerve atrophy, all suggesting Greig syndrome. The major symptom of this syndrome, the hypertelorism, varied considerably in its expressivity in the three siblings. This fact is normally taken into consideration in the diagnosis of Greig syndrome, but we suggest that an alteration in skull formation should be the criterion for the syndrome rather than extreme hypertelorism.

The term "hypertelorism" was introduced by Greig [10] to indicate an extremely enlarged distance between the eyes. Presently the meaning of the term has been extended to include any pathologically enlarged distance between the inner corners of the eyes [3, 15]. Several authors have proposed that the term "euryopia" should be used for an interocular distance which exceeds the upper limit of the normal range but does not reach extreme values (Table I) [5, 11, 16, 18]. Enlarged interorbital distance may occur [13]

as a rare incident within the normal variability of the population. Mean interorbital distances were found to vary between human races [8];

as a symptom of a number of hereditary and non-hereditary pathological conditions associated with defects in skull development. This may not necessarily be present. Leiber and Olbrich [16] cite "hypertelorism" in more than 70 different syndromes,

as the major feature of the syndrome described by Greig [10] (Synonyms: Greig's hypertelorism, familial hypertelorism). Walker [20] differentiated this "primary" hypertelorism from "secondary" hypertelorism. The former is a result of other defects of skull development such as frontal encephalocele and meningocele, or medial skull cleft (De Meyer syndrome). It should be pointed out that Greig syndrome has not always been properly understood: as already indicated, conditions with hyperteloric symptomatology, as well as secondary defects in development, have sometimes been classified as Greig syndrome. Moreover, reports of cases vary according to the major field of interest of their author [9, 14]. Most of the older reports dealing with Greig syndrome concentrated on analysing

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TABLE I

Normal and pathological values of the medial canthal Index and circumference-interorbital Index (Günther, 1933). Stenopia is an abnormally small interorbital distance, metropia is a normal interorbital distance and euryopia is an intermediate condition between metropia and hypertelorism

	Stenopic	Metropic	Euryopic	Hypertelorism
Medial canthal Index	28	28–38	38–42	42
Circumference-interorbital Index	4.5	4.5–6.8	6.8–8.0	8.0

the dominant feature of the syndrome, the hypertelorism neglecting the remaining symptomatology. The repeated simultaneous occurrence of certain characteristics in the head (hypertelorism, flattened nose bridge, upward palpebral fissure, divergent strabism, ear shape, eye fundus abnormalities), together with mental retardation, slight abnormalities of the extremities and cryptorchism, cannot be accidental. It may be concluded that the complex of pathological findings described by Greig does not represent an isolated defect of interorbital distance but is a syndrome in the full meaning of the word [3, 15, 16]. Thus, Greig syndrome should be understood as a complex of abnormalities, the major one being a defect in the development of the chondral skull basis. In this paper we describe a family with three siblings affected by this syndrome.

CASE REPORTS

After having each of their children, the parents repeatedly requested the paediatrician to explain the reason for the illness. They also asked him to estimate the risk for another child they might have.

The proband, J.K., was the youngest daughter born in 1976. Overall psychomotor development was retarded. Mental retardation with marked facial dysmorphy (marked hypertelorism with no epicanti present, broad and flattened nose bridge continuing directly into the forehead, characteristic supraorbital arches parallel to the eyebrows), divergent strabism, the ears larger and set lower than usual and rotated backwards were observed (Fig 1). Diastema was present between the first upper incisors. The skull made a brachycephalic impression. Neurological examination revealed dyscrania with hypertelorism and non-progressive atrophy of the optic nerves, hypertonic syndrome with a characteristic walk. X-rays of the skull showed signs of hypertelorism with an interorbital distance of 12 cm, slight antimongoloid position of the orbits. The internasal bone was absent. Anthropometric examination of the skull is summarized in Table II. Dermatoglyphic examination revealed that the main lines tended to run longitudinally, pattern intensity on palms was low, carpal triradius was in

the t-position and transversal flexion creases were absent. Cytogenetic examination of peripheral blood lymphocytes showed a normal female karyotype (46,XX). Ophthalmologic examination was not possible because the patient would not cooperate.

A sibling of the proband, M.K., was born in 1972. She had begun walking at the age of 18 months, after which walking development stopped for one year. She had been able to control her body functions since the age of 3 years, started to

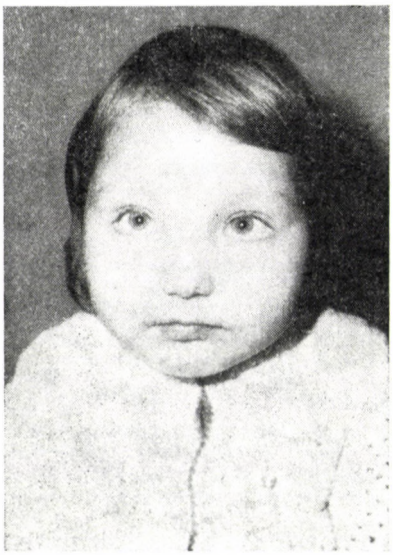

FIG. 1. Judita K. at 2 years of age

TABLE II

Anthropometric examination of the heads of the three siblings with Greig syndrome. (Results are expessed in mm; in parentheses, normal values for the corresponding age groups)

Parameters	Judita K. 1976	Monika K. 1972	Ladislav K. 1969
Head length (g-op)	145 (154)	142 (165.5)	164 (168)
Head breadth (en-en)	127 (133.6)	134 (142.4)	142 (146)
Forehead breadth (ft-ft)	100 (92.4)	100 (98.4)	110 (100)
Face width (zy-zy)	119 (106)	120 (116.4)	125 (118)
Bigonial width (go-go)	93 (81.9)	95 (88)	99 (90)
Physiognomic face height (tr-gn)	150	130	160
Morphological face height (n-gn)	90	100	117
Head circumference (g-op-g)	437 (474)	455 (500)	500 (510)
Medial canthal distance	38 (25.2)	35 (27.9)	31 (28)
Lateral canthal distance	94 (75.3)	92 (78.8)	98 (79)
Cephalic Index	87	94	86
Medial Canthal Index	40.4	38.04	31.6
Head-circumference-interorbital Index	8.4	7.7	6.2

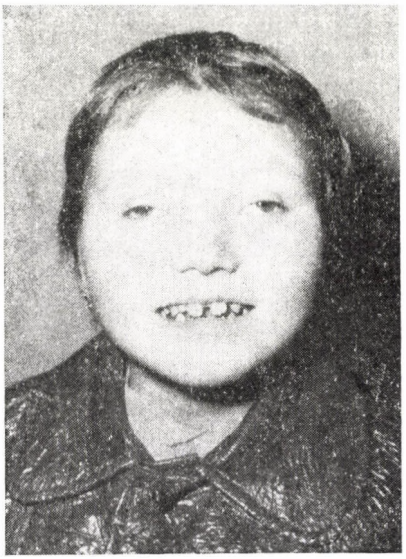

FIG. 2. Monika K. at 6 years of age

speak when she was 3 1/2 years old. At the age of 6 years her body weight was 16 kg, and length 105 cm. She was obviously mentally retarded with a characteristic facial dysmorphy, similar to that of her sister (enlarged interorbital distance without epicanthi, and a broad nose bridge, divergent strabism, large and lower set ears, Fig 2), diastema between the first upper incisors and flattened occiput. She had markedly larger and longer digits IV on her feet, nearly as large as digits II. Neurological examination gave similar results as those of her sister (mainly hypertonic syndrome and characteristic walk). X-ray of the skull showed that the distance between the outer orbital corners was 9 cm and the internasal bone was absent. Ophthalmological examination revealed that the otic disc was almost entirely discoloured, sited in level, the vascular gate was normal, arterioles and venules were all narrow, the peripheral retina showed no pathological changes, the macular reflex was absent, granular degeneration of the macular region was seen. Conclusion of the ophthalmological examination was: divergent strabism, macular degeneration, atrophia nervi optici in progression, nystagmus, hypertelorism. Anthropometric examination is summarized in Table II. Dermatoglyphic examination showed pattern frequencies in digits within the normal range. Total ridge count was normal (TRC = 135). Main lines tended to run longitudinally and pattern intensity on the palms was normal. The carpal triradius was in the t-position. Transversal flexion creases were absent. Chromatographic examination of the urine showed normal findings. Cyto-

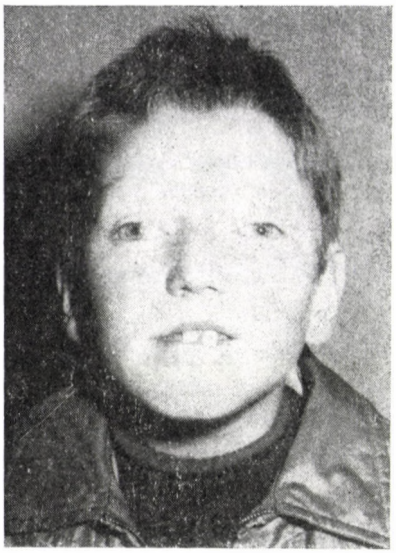

FIG. 3. Ladislav K. at 9 years of age

genetic examination of peripheral blood lymphocytes showed the normal female karyotype 46, XX.

The eldest brother L.K. of the proband was born in 1969 from the first pregnancy of a 19-year-old mother and a 27-year-old father. His overall psychomotor development was retarded. He had begun walking at the age of 2 years, controlling body functions at the age of 2 1/2 years and speaking at the age of 3 years. Physical examination of the 11-year-old boy showed mental retardation. He spoke in an unclear inarticulate manner. A marked facial dysmorphy was present (of the same type as that of his younger siblings) (Fig. 3) with slightly larger interorbital distance and broad nose bridge, divergent strabism, larger and lower-set ears, mouth often open, diastema between the first two incisors in the upper jaw. All the teeth were yellow and carious (he had often been treated with tetracycline), hypoplastic external genital organs with slack testes and clinodactylia on digits V of both hands. Neurological examination gave similar results as those of his younger siblings, mainly signs of hypertonic syndrome with a resulting characteristic walk. X-ray of the skull showed that the distance between the outer orbital corners was 10 cm. There were no other pathological signs, apart from an absent internasal bone. Ophthalmological examination disclosed discoloured papillae of the optic nerve in level, pigmented nasal conus, atypical vascular gate, slightly blunt and narrow branching of the vessels, pigmentation of the equatorial portion of the retina mainly on its periphery resembling pigment degeneration of the retina. Due to the disturbed

central fixation, both eyes had alternate divergence and there was total failure of focussing capacity. Anthropometric examination revealed a cephalic index of 86, i.e. hyperbrachycephaly. Neurocranium dimensions were below the normal range.

Discussion

Table III shows that the complete symptomatology of Greig syndrome was found in the youngest sibling. The canthal index did not reach the one agreed between euryopia and hypertelorism. However, as the child was only 3 years old at the time of examination, the head circumference/interorbital distance, which was clearly in the hyperteloric range, might be considered more reliable. Other symptoms of Greig syndrome included brachycephaly, serious mental retardation, divergent strabism, characteristic shape of the nose bridge and of the forehead, rotated low set ears with diasthema in the upper teeth, missing internasal bone and hypertonic syndrome. The eye fundus could not be examined as the patient did not cooperate.

The question then arose, how should the two elder siblings be classified ? They had all other symptoms including positive findings in the eye fundus that are characteristic of Greig syndrome, but they did not fulfil the criterion for hypertelorism. Should a diagnosis of Greig syndrome be made without the presence of extreme hypertelorism ? In fact, this has already been suggested by Günther [12] who stated that the constitutional abnormality of skull formation described by Greig does not always result in ex-

Table III

Symptomatology of the three siblings with Greig's syndrome

Symptomatology	Judita K. 1976	Monika K. 1972	Ladislav K. 1969
Mental retardation	++	++	++
Brachycephaly	++	+++	++
Microcephaly	+—	+	+—
Neuro-viscerocranium ratio	+	++	+—
Canthal Index	Euryopia	Euryopia	Normopia
Head-circumference-interorbital Index	Hypertelorism	Euryopia	Normopia
Absence of internasal bone	+	+	+
Diasthema in upper teeth	+	+	+
Atrophy of optic nerve	n.d.	+	+
Degenerative alterations of retina	n.d.	+	+
Hypertonic syndrome	+	+	+
Wide nasal bridge	+++	++	+
Enlarged set lower than usual	+	+	+
Others		Enlarged digit IV on feet	Clynodactily, genital hypoplasia, slightly open mouth

treme hypertelorism, and this leads to difficulties in diagnosis of certain cases. In familial occurrence with all other symptomatology suggesting constitutional skull abnormality there may be a decreased expressivity. This could be the case for the two eldest siblings: M.K. with an euryopic interorbital distance, and her brother L.K. with an interorbital distance within the normal range. The variability of findings of intercanthal distances in three siblings with identical, likely hereditary, developmental defects turns our attention to the importance of a defective skull formation rather than to extreme hypertelorism, the latter being purely a result of this prenatal defect.

It may be concluded from our observations that the diagnosis of the syndrome which has hypertelorism among its symptoms should be based on the establishment of a developmental defect of skull formation rather than on dimensions or indices; these should only be an aid to orientation. Aetiologically, the enlarged interorbital distance may be secondary to two kinds of defect [15]:

1. Defective development of the prechondral skull basis; here a number of neurological defects including Greig syndrome may be classified;

2. An early onset of pathological pressure inside the skull [11], as e.g. in Crouzon syndrome and Apert syndrome. Up till now, a condition for the Greig syndrome has been that hypertelorism should be "primary" and not secondary to another defect (e.g. to cleft defects). In our opinion, hypertelorism is secondary to a certain basic defect (depression or stimulation of growth of certain points of skull formation). Thus, the extent of hypertelorism as a result of such a defect may vary. This could explain the variable expressivity of hypertelorism and all the other symptoms in the three siblings. Basically, the entire complex process of postnatal skull formation is genetically determined. Several defects may, however, occur in this process caused by various external factors, leading to morphological alterations which when exceed the agreed limits are considered pathological. Günther [12], dealing with differential diagnostics of Greig syndrome and e.g. Crouzon syndrome, states as one feature the sporadic incidence of the former. Reports have, however, published on familial accumulation with possible autosomal dominant pathway over several generations [1, 6, 7, 19]. Families with suggested autosomal recessive heredity have also been reported [17].

Analysis of this family suggests an autosomal recessive heredity. The wide variability associated with Greig syndrome, the various modes of inheritance, and especially the mechanism of the pre- and postnatal development of these parts of the skull, suggest a heterogeneity in aetiology, pathogenesis and morphology of the observed clinical picture. Taking these facts into account, nosological entities associated with hypertelorism should be formed with extreme caution. For practical purposes of genetic counsel-

ling the genetic risk should primarily be based on analysis of the actual situation of the family, taking into account the possibility of decreased expressivity of individual symptoms as describied in this paper.

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