Median Cerebrofacial Dysgenesis: The Syndrome of Median Facial Defects with Hypotelorism

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Two patients with almost identical *median facial defects* are described. Both patients manifested a pure Pitressin responsive *diabetes insipidus*. These two patients are part of a graded series of *median cerebrofacial malformations* with *orbital hypotelorism*, which have been grouped under the heading of *Median Cerebrofacial Dysgenesis*. A revised classification of this group of anomalies is presented. The importance of distinguishing this group of patients from the group with the *Median Cleft Face Syndrome* with *hypertelorism* is stressed.

Careful attention to *face-brain relationships* will help elucidate our understanding of the embryogenesis of the facial region, and extend the number of diagnostic facies which currently can be recognized.

The central part of the face and forebrain are closely connected in early development, and when certain median facial defects occur, there is invariably concommitant maldevelopment of the anterior part of the brain. Since the arrest in cerebral development can occur at successively later stages of embryogenesis, a spectrum of various related gradations and combinations of median cerebrofacial anomalies is encountered.

In 1892 Kundrat used the term "arhinencephaly" to describe this spectrum of congenital forebrain malformations of varying severity. This term was used to describe the absence of the olfactory bulbs and tracts, which he believed to be the basic defect. However, although these structures are invariably absent, the cerebral anomaly is now known to be more extensive, the fundamental defect being a developmental failure of forebrain cleavage into lobes and ventricles. The term "Holoprosencephaly" was used by De Myer and Zeman (1963) to describe this arrest in cleavage of the prosencephalon (primitive forebrain vesicle) into cerebral hemispheres and to emphasize the holistic, primitive nature of the undivided prosencephalon. These terms, however, refer to the cerebral defects which are identified only at autopsy and make no reference to the significant median facial deformity invariably present.

The term "Median cerebrofacial dysgenesis" was suggested by Brucker et al. (1963) to describe this spectrum of anomalies. We feel that this is a more suitable descriptive designation, stressing, as it does, the facial as well as the associated cerebral defects. This term describes the whole spectrum of deformities, from the most severe form, cyclopia, through intermediate stages of decreasing severity, where the embryogenesis is arrested at succeedingly later stages, as the cerebral and facial development approach normality. The characteristic facial patterns at the severe end of the spectrum, such as cyclopia, ethmocephaly, or cebocephaly, always predict a severe, highly characteristic brain anomaly. (De Myer and Zeman, 1963; Yarkovlev, 1959). In the intermediate and more normal end of the spectrum, there is far less understanding of the patterns of facial anomalies and their predictive significance for the brain.

The two extremely interesting and instructive cases described in this paper fall into this end of the spectrum and reveal a diagnostic facies, which has not, to our knowledge, previously been described in the literature.

Patient 1

This two-month-old baby was referred to the Plastic Surgery Unit at The Hospital for Sick Children, London, for repair of her cleft

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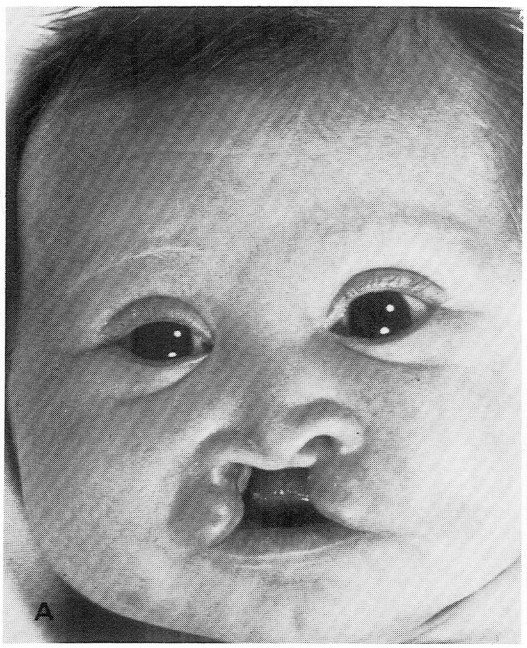

FIGURE 1a. Patient 1. Note the orbital hypotelorism, flat nasal bridge, and right sided cleft of primary palate with partial absence of central intermaxillary segment.

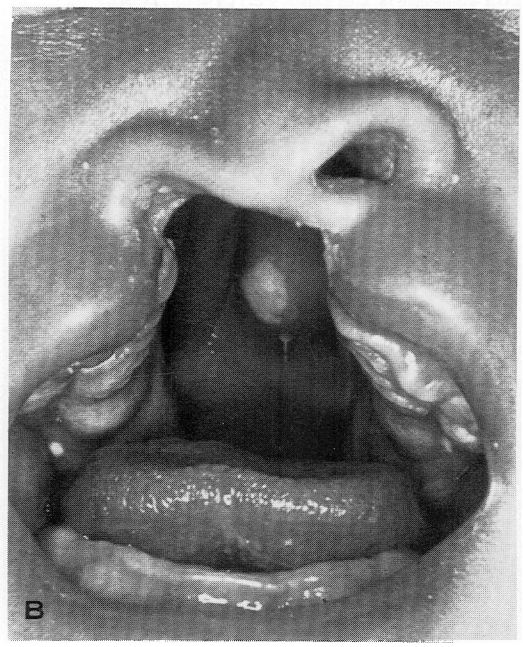

FIGURE 1b. Patient 1. Close-up view of defect. Note flat nasal bridge and absence of cartilagenous nasal septum. Remnant of central intermaxillary segment represents the prolabium-premaxilla anlage. There is wide cleft of secondary palate.

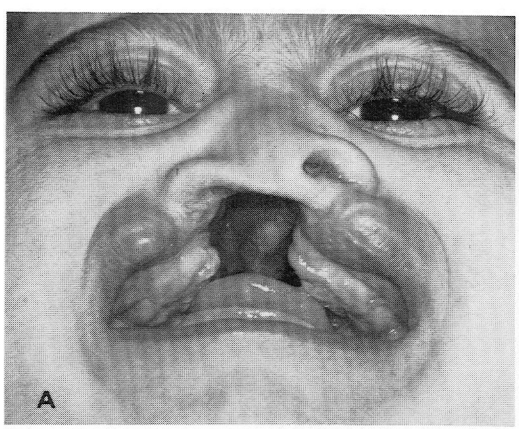

FIGURE 2a. Patient 2. Note similarity of facial features in Patient 1 and 2. Orbital hypotelorism, flat nasal bridge and unilateral cleft of primary palate is present.

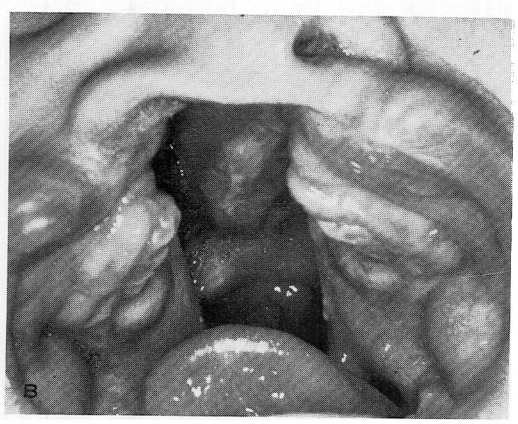

FIGURE 2b. Patient 2. Close up view showing partial absence of central intermaxillary segment and absence of anterior portion of nasal septum. Prolabium-premaxilla anlage and wide cleft of secondary palate are evident.

lip and palate. She was born at full term after an uncomplicated vertex delivery. The eighteen-year-old mother was unmarried and had had an uneventful pregnancy during which no drugs had been taken. There was no pertinent family history on the mother's side. The paternal history could not be ascertained.

At birth, the patient was noted to be hypotonic with a head circumference of 31.5 cms. She subsequently required tube feeding and was slow to gain weight.

The facial malformations shown in Figure 1 were present. Pupils were normal in size, reacted to light, and had no coloboma or

other defect. Fundoscopic examination was unremarkable. Her skull did not transilluminate. Electroencephalography showed a moderate abnormality with irregular slow and sharp elements in the temporal region.

Echoencephalography failed to detect any midline interhemispheric division. Skull roentgenograms showed the characteristic features present in Figure 3 with an interorbital distance (I.O.D.) of 1.1 cm. Normal I.O.D. for this age is 1.6 cms. (Currarino and Silverman, 1960). Chromosome studies and dermatoglyphics were normal. The only extracephalic abnormality present was a bilateral congenital dislocation of the hip.

At the age of three months, the lip defect was closed with a quadrilateral flap repair with wide undermining on both sides of the defect.

Post-operatively, the patient developed hypertonic dehydration, and urine osmolality was found to be inappropriately dilute as compared with plasma osmolality. She was unable to concentrate her urine on prolonged water deprivation, but urine osmolality concentrated to 640 m. osmols/kg, 9 hours after the injection of eight units I.U. of Pitressin. All other studies of endocrine and renal function were within normal limits. A diagnosis of Pitressin responsive diabetes insipidus was made. She was given a low sodium milk plus supplements, and on this regime it was possible to control the osmolality of the plasma with reasonable success.

Subsequent to discharge from the hospital, her psychomotor development was slow, and she suffered from occasional convulsions. At the age of 14 months, she was re-admitted for cleft palate closure, but in view of her slow development and poor medical condition it was decided to defer the operation. The patient is now 18 months of age with a poor prognosis for future development.

Patient 2

This patient was referred to The Hospital for Sick Children, London, at the age of 9 months for repair of a cleft lip and palate. He had been born in Kuwait, the third child of healthy parents, who were first cousins. The two other siblings were healthy. There was no family history of cleft lip or palate or any other illness. The pregnancy and delivery were normal and there were no known illnesses or medications taken during the pregnancy.

The child had been difficult to feed because of the cleft palate. At seven months of age,

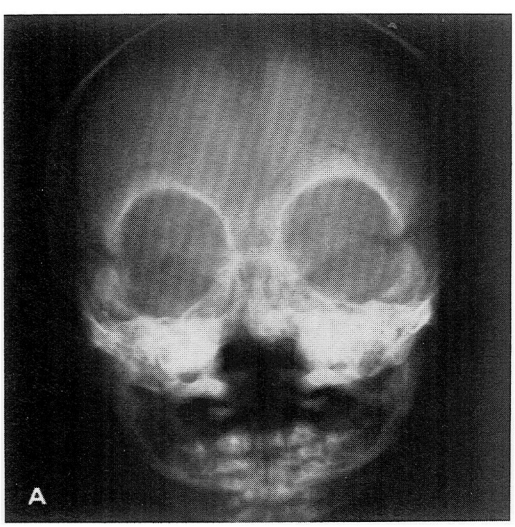

FIGURE 3a. Patient 1. Frontal roentgenogram indicates orbital hypotelorism with hypoplasia of nasal and median facial bones. Longest diameters of the orbits are vertically oriented and contour of superior margins is semicircular ("half moon"). Note wide distance between palatal shelves and presence of Microcephaly.

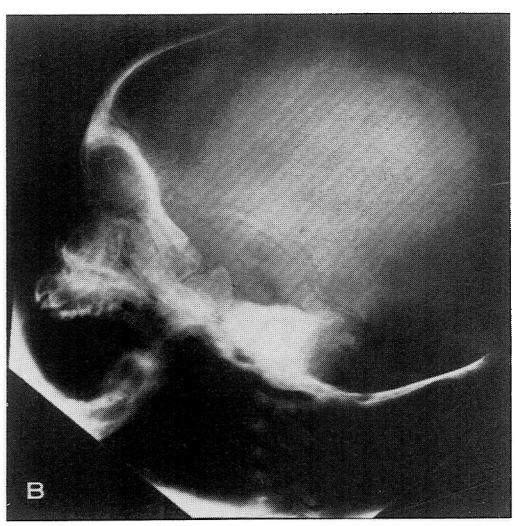

FIGURE 3b. Patient 1. Lateral roentgenogram indicates small frontal bones, small anterior cranial fossa, high orbital roof and maxillary bone hypoplasia. Hypoplastic sella turcica and patent craniopharyngeal canal are present.

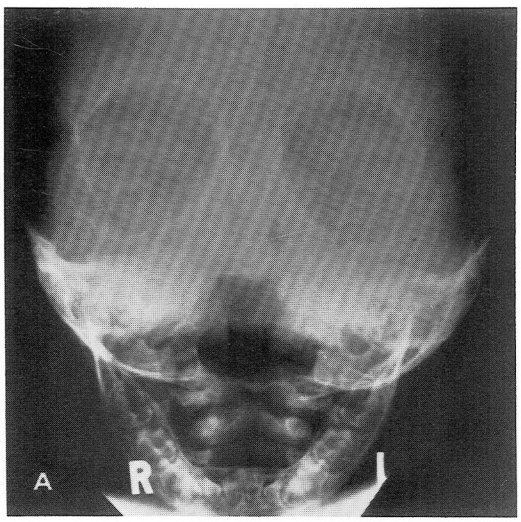

FIGURE 4a. Patient 2. Frontal roentgenogram demonstrates similar radiological features as in Patient 1. Orbital Hypotelorism, microcephaly and hypoplasia of median facial bones are present. Longest diameter of the orbits are convergent superomedially.

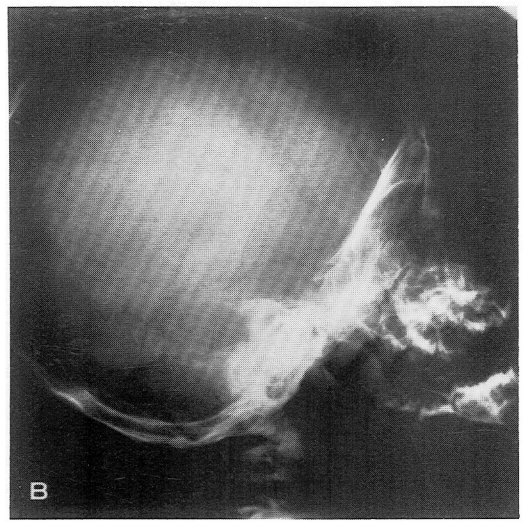

FIGURE 4b. Patient 2. Lateral roentgenogram demonstrates strikingly similar features to patient 1. Note the small, maldeveloped sella turcica and shallow orbits. Very small frontal bones and anterior cranial fossa are present.

the cleft lip was repaired in Kuwait. The repair had subsequently broken down. Post-operatively, the patient had apparently been unwell and intravenous fluids had been given.

The facial malformations shown in Figure 2 were present. Microcephaly, with the head circumference less than the third percentile, was evident. There were no extracephalic abnormalities present. Ophthalmological examination was unremarkable. There was no transillumination of the skull. Electroencephalogram response suggested mildly altered brain function with no localising features. Echoencephalography failed to detect a midline interhemispheric division. Chromosome studies and dermatoglyphics were normal. Skull roentgenograms showed the features present in Figure 4, with an I.O.D. of 1.25 cms., the normal for this age being 1.8 cms. (Currarino and Silverman, 1960).

The cleft lip was repaired in a similar fashion to the first patient, using a quadrilateral flap with wide undermining on both sides of the defect.

Two days post-operatively, the patient became irritable, started to vomit, and was found to have hypertonic dehydration, with the urine osmolality inappropriately dilute when compared with the plasma osmolality. Response to water deprivation and pitressin stimulation once again revealed the presence of Pitressin responsive diabetes insipidus. Renal function and all other endocrinological testing were within normal limits.

Initially the patient was treated with intramuscular injections of Pitressin tannate, but eventually, on a fluid intake of 170 ml./Kg/day without added salts or Pitressin, normal blood electrolyte and osmolality levels could be maintained.

A year later the patient was readmitted for repair of the cleft palate. During the year following the lip repair, the patient's psychomotor development had been poor. There had been frequent convulsive episodes, which at times had been uncontrollable. Careful preoperative assessment was performed, and the considerable operative risk was explained to the parents, who were, none-the-less, keen that the defect be closed. Twenty-four hours after an uneventful repair of the cleft palate, the patient suffered a cardiac arrest and died. Post-mortem examination was refused by the family as they were Muslims, and the anticipated cerebral defects could not be corraborated.

Discussion

Both of these infants exhibit remarkably similar cerebrofacial and endocrinological

anomalies. The presence of microcephaly, orbital hypotelorism, flat nasal bridge, absent anterior portion of the nasal septum, right sided unilateral cleft of the primary palate (Stark and Ehrmann, 1958) with a hypoplastic prolabium-premaxilla, and a bilateral wide cleft of the secondary palate (Stark and Ehrmann, 1958) was common to both infants. Similarly both infants manifested psychomotor retardation and a pitressin responsive diabetes insipidus.

To understand the evolution of these striking anomalies and their place in the spectrum of related cerebrofacial defects, a brief review of the basic embryology is essential.

Embryology

The embryology of the forebrain and the median aspect of the face are closely connected. Embryological failure may result in a spectrum of cerebral defects ranging in severity from alobar, through semilobar to lobar holoprosencephaly in association with a corresponding spectrum of mid-facial defects.

This association is explained by the dual role of the precordal mesoderm. (Yarkolev, 1959; Mettler, 1947). Its first role is in the formation of the median skeleton of the face, producing the ethmoid and crista galli, vomerine and nasal bones, and the cartilagenous nasal septum and premaxilla. Its second role is in the induction of the rostral neural ectoderm and, thereby, prosencephalic development. Thus, when precordal mesoderm is defective, mid-facial and prosencephalic development may be arrested at any stage (De Myer et al., 1964). The deformities exhibited by these two infants could be explained by defective development in these concurrent embryological events. The unilateral complete cleft of the primary palate with a hypoplastic prolabium, premaxillary segment, is probably a result of a partial failure of the precordal mesoderm, in particular the mesoderm which should have formed the right half of the primary palate or the right nasomedial process. The concommitant mid-facial skeletal deformities and forebrain abnormalities were also present, giving rise to a diagnostic cerebrofacial deformity which, to our knowledge, has not previously been described.

The pituitary gland, embryologically, is formed from the union of Rathke's pouch, arising from the primitive pharynx and eventually giving rise to the anterior lobe, and the infundibular process from the floor of the diencephalon, which eventually forms the posterior lobe. The important process for normal development seems to be fusion of Rathke's pouch with the infundibular process (Kingsbury and Roemer, 1940; Gilbert, 1935; Reid, 1960). The hypothalmic and infundibular region is the area of the brain embryologically most closely related to the precordal mesoderm, and is thus almost always severely affected in the genesis of the holoprosencephalic brain. The antidiuretic hormone is formed in the cells of the supraoptic and paraventricular nuclei of the hypothalamus and travels down the neural pathways of the supraopticohypophyseal tract to the posterior pituitary where it is stored until released into the circulation after appropriate stimuli (Leveque and Sharrer, 1953). The pure pitressin responsive diabetes insipidus manifested by the two infants in the absence of any anterior pituitary or other endocrinological abnormalities could be explained on the basis of disordered fusion, formation, transport, or storage related to the concomitant defect in the precordal mesoderm.

The presence of the pitressin-responsive diabetes insipidus in the syndrome of median cerebrofacial dysgenesis is not surprising in view of the preceding discussion. However, prior to the two cases reported in this paper, only one previous case had been reported in the literature (Hintz et al., 1968).

Differential Diagnosis

It is important to determine the degree of holoprosencephaly since the prognosis for psychomotor development and survival beyond infancy is dependent on it, and this, in turn, will influence the management of the facial defects. The degree of holoprosencephaly can be predicted from the appearance of the median facial anomalies which extend through an unbroken spectrum from the most severe degree of the malformation, Facies 1, through Facies IV and to the normal face (De Myer, 1971). (See Figure 5.) De Myer and his colleagues, following a review of 75 cases in the literature and personal study of 14 cases with Facies I to IV, found, in every case without exception, that these patterns of median facial anomalies, when present, predicted the holoprosencephalic brain, which was almost in-

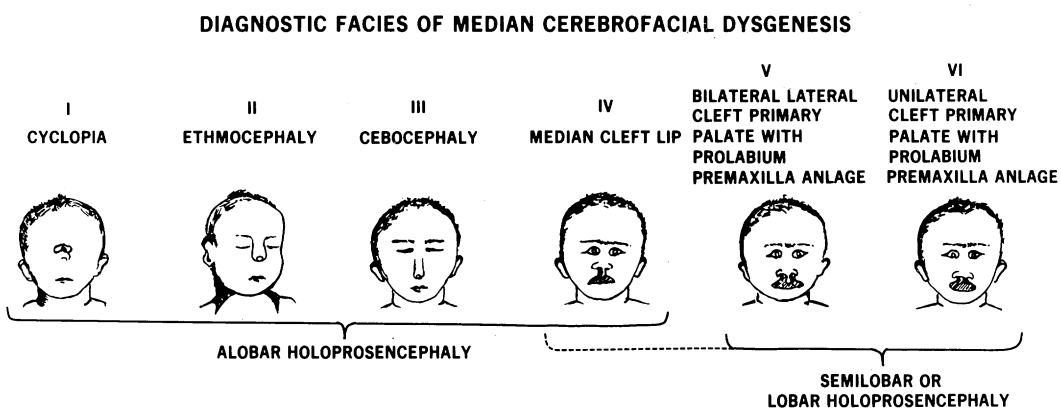

FIGURE 5. Composite diagram of the diagnostic facies of the Median Cerebrofacial Dysgenesis Syndrome.

variably of the alobar type. The face thus predicts the brain (De Myer and Zeman, 1963; De Myer et al., 1964; De Myer, 1971). For Facies V and VI, there have been too few examples described to permit a strong formulation of face-brain relationships. From Facies V to the normal face and brain is a small step, and the face-brain correlation may weaken at this level (De Myer, 1964).

It is Facies IV to VI that are of prime interest to the plastic surgeon because all three have characteristic mid-facial anomalies which include clefts of the primary palate and, often, of the secondary palate. Orbital hypotelorism is invariably present (De Myer et al., 1964; Currarino and Silverman, 1960). In Facies IV, there is a total absence of the primary palate, giving rise to a complete median cleft lip. The lateral lip segments have the same configuration as in ordinary cases of bilateral lateral cleft lip, and this has led some authors to describe this as a bilateral complete lateral cleft with absent prolabium and premaxilla (Brucker et al., 1963).

In Facies V, a rudimentary intermaxillary segment consisting of the prolabium and premaxilla is present, giving rise to a bilateral complete lateral cleft of the primary palate with rudimentary intermaxillary segment or prolabium-premaxillary anlage. In Facies VI, the category newly described in this paper, there is a unilateral complete cleft of the primary palate with a prolabium—premaxillary anlage. The term philtrum-premaxillary anlage (De Myer et al., 1964) has been changed to prolabium—premaxillary anlage, for as Ivy (1962) pointed out "the term philtrum should be limited to the vertical groove in the middle of the upper lip, while the prolabium includes not only the middle groove of philtrum but also the full thickness of lip tissue on either side of the groove. It is possible to have a prolabium without a philtrum."

This whole spectrum of median facial defects with orbital hypotelorism, from Facies I to VI, has been grouped together under the heading Median Cerebrofacial Dysgenesis. This must be distinguished from the other distinct and separate syndrome also associated with midline facial anomalies i.e. the median cleft face syndrome with orbital hypertelorism (De Myer, 1967; Kurlander et al., 1966; Francesconi and Fortunato, 1969; Edwards et al., 1971). In this syndrome, the embryogenesis and clinical features are different, and the brain is usually normal. These children have a normal life expectancy and in most cases, normal or only mildly impaired intelligence (De Myer, 1971; De Myer, 1967).

Prognosis and Management

The poor prognosis in this group of infants parallels the severity of the cerebrofacial anomaly, and the potential for survival and psychomotor development will influence the subsequent management.

Few of these patients will survive through infancy (De Myer and Zeman, 1963; De Myer et al., 1964; De Myer, 1971; Millard and Williams, 1968), and surgery must be carefully considered in view of the poor prognosis. Patients with Facies I to IV have no developmental potential and usually die within the first year of life. Facies V and VI may show some psychomotor development, but will usu-

ally be severely retarded. Occasionally patients with lobar holoprosencephaly will survive infancy and childhood, and, although most will be mentally retarded, some will have sufficient intelligence to live freely in society (De Myer and Zeman, 1963).

Surgical closure of the lip defect can be considered to improve the aesthetic appearance of the face and to facilitate social acceptance and feeding. Millard and Williams (1968) described the use of an Abbe flap to close the lip defect. In the two patients described in this paper, a large quadrilateral flap was used to close the defect. Major facial reconstruction is rarely warranted.

Convulsions, difficulty with feeding and temperature control are other problems faced in the management of these patients. Various endocrine deficiencies if present, may have to be treated.

Genetic counselling of the parents is an important final consideration. A positive family history of related defects has been reported (Hintz et al., 1968; De Myer et al., 1963). According to De Myer (1971), once a child with medial cerebrofacial dysgenesis has been born, the risk of another affected child is increased.

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