Five Cases of DeMyer Sequence: An Interophthalmic Dysplasia

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Five cases with vomero-septal-prolabium agenesis, four with premaxillary agenesis, and one with hemipremaxillary agenesis are presented. All five patients had complete clefts of the secondary palate. No known family history for craniofacial dysmorphia was reported. Height and weight ranged from 2nd to 10th centile. Psychological testing showed intelligent quotients of 121, 93, 72 for three patients; two were microcephalic with undetermined IQ, but severe generalized developmental delay. CT scans for the patient with the IQ of 72 and for one of the two microcephalic subjects showed normal brain structures. The other microcephalic patients had midline prosencephalic dysgenesis. Cephalometric analysis of the cranial base and interorbital dimension using normal standards and self indexing showed hypotelorism and small anterior cranial bases to be apparently related to reduced size of the sphenoid. An intact ethmoid, nasal bone, and crista galli appear to represent key anatomic differences in these patients as compared to classical holoprosencephaly sequence subjects. It was suggested that this pattern of midline facial agenesis may range from a solitary central incisor to the most severe variant presented. Using the embryologic classification, these subjects fall best under the heading of craniofacial dysplasia rather than cerebral craniofacial dysplasia, as a different type of interophthalmic dysplasia or DeMyer sequence.

KEY WORDS: *holoprosencephaly, DeMyer sequence, cleft lip, cleft palate, microcephaly, midline cleft, septo-optic dysplasia*

True median facial clefting is often associated with holoprosencephaly. In 1964, DeMyer et al presented a spectrum of holoprosencephalic cases and hypothesized that the face predicts the brain. In 1975, DeMyer suggested that hypotelorism of more than 2 standard deviations below the mean denotes a very high risk for an abnormal brain and that total aplasia of the intermaxillary segment was incompatible with life beyond infancy. Cohen and Hohl (1976) demonstrated that holoprosencephaly has a facultative rather than an obligatory relationship with median facial dysmorphia and that holoprosencephaly and midline facial dysmorphia are etiologically heterogeneous. As reported by van der Meulen et al (1983), the term "cleft" is misleading when applied to malformations characterized by the aplasia found in midline facial anomalies. Van der Meulen et al (1983) proposed an embryologic classification according to the location and time of developmental arrest for craniofacial malformations that they labeled "dysplasias." Van der Meulen et al (1983) subdivided craniofacial malformations into cerebral craniofacial dysplasias and craniofacial dysplasias as suggested by Vermy-Keers et al (1983). Van der Meulen et al (1983) classified all patients with an absence or severe hypoplasia of the premaxillary, nasal, and lacrimal bones, nasal septum, and the ethmoid with crista galli under the heading of interophthalmic dysplasia and hypothesized that such defects in combination with hypotelorism are pathognomonic of a brain that has failed to divide into intact cerebral hemispheres.

In a comprehensive review of holoprosencephaly and related midline cerebral anomalies, Leech and Shuman (1986) proposed a simple pathogenetic mechanism sharing defects of midline prosencephalic growth. Leech and Shuman (1986) suggested a category of midline prosencephalic dysgenesis including aprosencephaly, holoprosencephaly, septo-optic dysplasia, and corpus callosum agenesis based on the developmental association between the face and the brain. However, Leech and Shuman (1986) reported that the em-

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phasis placed on the severe median facial malformations may have slowed recognition of the spectrum of brain anomalies.

There appears to be at least a semantic problem in classifying patients with median facial and cerebral dysgenesis. Nevertheless, any classification scheme should clearly recognize that median facial dysmorphia and midline prosencephalic dysgenesis are heterogeneous in nature. Jaramillo et al (1988) suggested the term "DeMyer Sequence" to include both categories of malformation. The semantic puzzle might be resolved by the embryonic classification of van der Meulen et al (1983) by defining interophthalmic dysplasia as either a cerebral dysplasia or a craniofacial dysplasia. The problem with the term "holoprosencephaly sequence" is that cases without any evidence of holoprosencephaly are found in this class of malformation.

The delineation of midline facial dysgenesis may be incomplete because of inadequate diagnostic methods and because individuals with similar physical appearance may have distinctly different midline cerebral anatomy. The purpose of this report is to propose a categorization based on data from five cases with midline facial anomalies including descriptions of craniofacial morphology as assessed by cephalometric radiographs. Skeletal findings will be related to anomalies of the central nervous system.

Case 1

This 5 pound, 13 ounce white female was born after an 8.6-month gestation to a 23-year-old father and 22 year-old-gravida 1, para 1 mother. There was a 2½-year-old male sibling. A maternal cousin was known to have cleft palate. At birth, the following anomalies were found: median cleft lip; cleft palate; absence of the premaxilla, vomer, and nasal septum; absent columella; and a nasal tip tethered down to the left labial segment (Fig. 1). At 3 years of age, hypotelorism, a balanced facial profile (Fig. 2), and Class II molar occlusion with anterior medial positioning of the lateral segments was noted. Head circumference was below the 2nd centile.

Height and weight were below the 5th centile. Bone age studies done at 5 years, 6 months of age were reported as consistent with a 2-year, 8-month to 3-year-old girl. At this time, growth hormone studies (somatomedin, T_3, T_4, TSH) were found to be normal. The endocrine diagnosis was constitutional delay of growth.

Age appropriate standard and case values were corrected to zero magnification for cephalometric analysis. At age 58 months, interorbital distance was 15 mm, 2 standard deviations (SD) below the mean for unilateral cleft lip/palate subjects (Ishiguro et al, 1976). Sella-nasion (SN) at 52.2 was 3 standard deviations below the mean (Broadbent et al, 1976). The ethmoid (SE, spheno-ethmoid registration to NMF, naso-maxillo-frontal suture) was normal, but the sphenoid (S-SE) at 18 mm was 78 percent of template (T) norm of 23 mm (Broadbent et al, 1976).

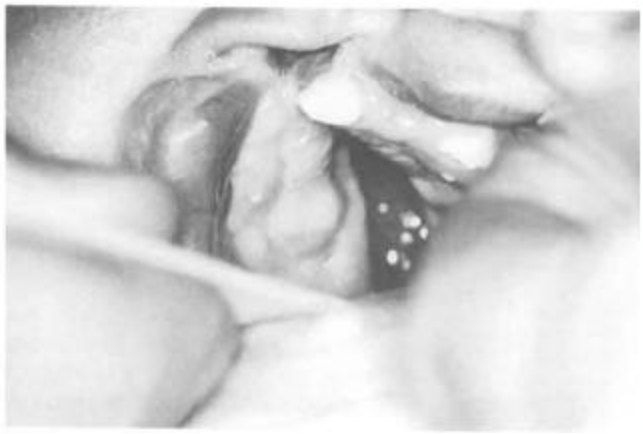


FIGURE 1 Intraoral view of Case 1 at 1 year of age.

Cognitive ability was evaluated as part of a psychological battery administered to rule out attention deficit disorder (ADD) at 7 years, 11 months of age. Using the Wechsler Intelligence Scale for Children, Revised, a Verbal Scale IQ of 97 (42nd centile), a Performance Scale IQ of 91 (27th percentile), and a Full Scale IQ of 93 (32nd percentile) was obtained, which placed her overall level of intellectual functioning in the normal range. Both parents were of normal intelligence and high school graduates. Attention deficit disorder (ADD) was diagnosed during her psychological evaluation, and she was placed on Ritalin, 5mg twice daily on school days. She received resource room help at school for reading and math because the psychologist thought she was borderline learning disabled. She achieved Bs and Cs in the 4th and 5th grades. No eye examinations were obtained. No CT imaging was obtained for this patient. Smell was reported to be functional, but no specific testing was done.

Case 2

Case 2 was a full-term 6 pound, 12 ounce white female born to a 28-year-old father and 26-year-old, gravida 1, para 1 mother. There was a normal 2 year-old-brother. There was no known family history of clefting or other craniofacial malformations. The mother had influenza in the third month of gestation. At birth, head circumference and body length were just below the 50th centile and weight was at the 30th centile. General physical examination was essentially normal except for the cleft. At 4 years of age height and weight were at the 10th centile. Growth hormone studies were normal. Bone age studies done at 10 years, 1 month of age revealed an approximate bone age of 9 years.

Cephalometric analysis at 43 months of age showed an interorbital distance 3 SD below the mean (Ishiguro et al, 1976). SN was 2 SD below the mean; the sphenoid (S-SE) of 20 mm was 87 percent of normal, but the ethmoid (SE-NMF) was normal (T; Broadbent et al, 1976).

At 3 years, 7 months of age hypotelorism was evident (Fig. 3). A Class I malocclusion was present with normal relationship of the cleft segments and modest medial displacement of the cuspids. The lateral cephalogram demonstrated obvious hypoplasia of the premaxilla with a single central incisor and no vomer. The posterior-anterior cephalogram showed evidence of hypoplasia of the median septal structures. The crista galli was visible (Fig. 4).

Cognitive assessment at 6 years of age (Wechsler Preschool and Primary Scale of Intelligence) showed a Verbal Scale IQ of 121, a Performance Scale IQ of 116, and a Full Scale IQ of 121 placing her within the superior range of intellectual functioning. No evidence of ADD was noted. Oral language skills were above average based on evaluation by a speech-language pathologist. A CT scan was not indicated for this patient based on her intellectual levels and neurologic and developmental integrity. Smell was reported to be functional. Ophthalmologic examination was done at 4 years, 11 months and showed hyperopia (20/30).

Case 3

This black female, born to a 20-year-old primigravida alcoholic mother, was 5 pounds 15 ounces at birth. Delivery was normal. There was no known family history of clefting. At 3 months of age, complete absence of the premaxilla and columella and agenesis of vomeroseptal structures were noted. The nose was flat and hypoplastic without central support and the eyes were structurally normal but hypoteloric (Fig. 5). The diagnosis of fetal alcohol syndrome was applied.

The patient had primary lip repair at 3 months of age and had postoperative feeding problems including aspiration, periods of severe coughing, and cyanosis. General physical examination was normal. Radiographic examination of the chest revealed normal heart size, cardiovascular, and mediastinal structures. An inguinal hernia repair was done at 2 years of age. She also had an ophthalmologic examination at 25 months of age and was found to have normal vision.

At 4 years, 9 months of age, physical features included hypotelorism, a balanced facial profile, and a Class II malocclusion with relatively normal placement of the cleft segments. The lateral cephalogram showed obvious agenesis of the premaxilla but a basically normal horizontal maxillomandibular relationship. The posterior-anterior cephalogram showed the agenesis of the septum and premaxilla and presence of the crista galli. A CT scan done at 20 months of age was unremarkable.

In a cephalometric study at age 57 months, the interorbital distance was 2 SD below the mean (Ishiguro et al, 1976). SN was reduced more than 3 SD; the sphenoid, S-SE 18 mm was 78 percent of norm 23 mm, and the ethmoid, SE-NMF at 26 mm was 93 percent of the norm of 28.8 mm (Broadbent et al, 1976).

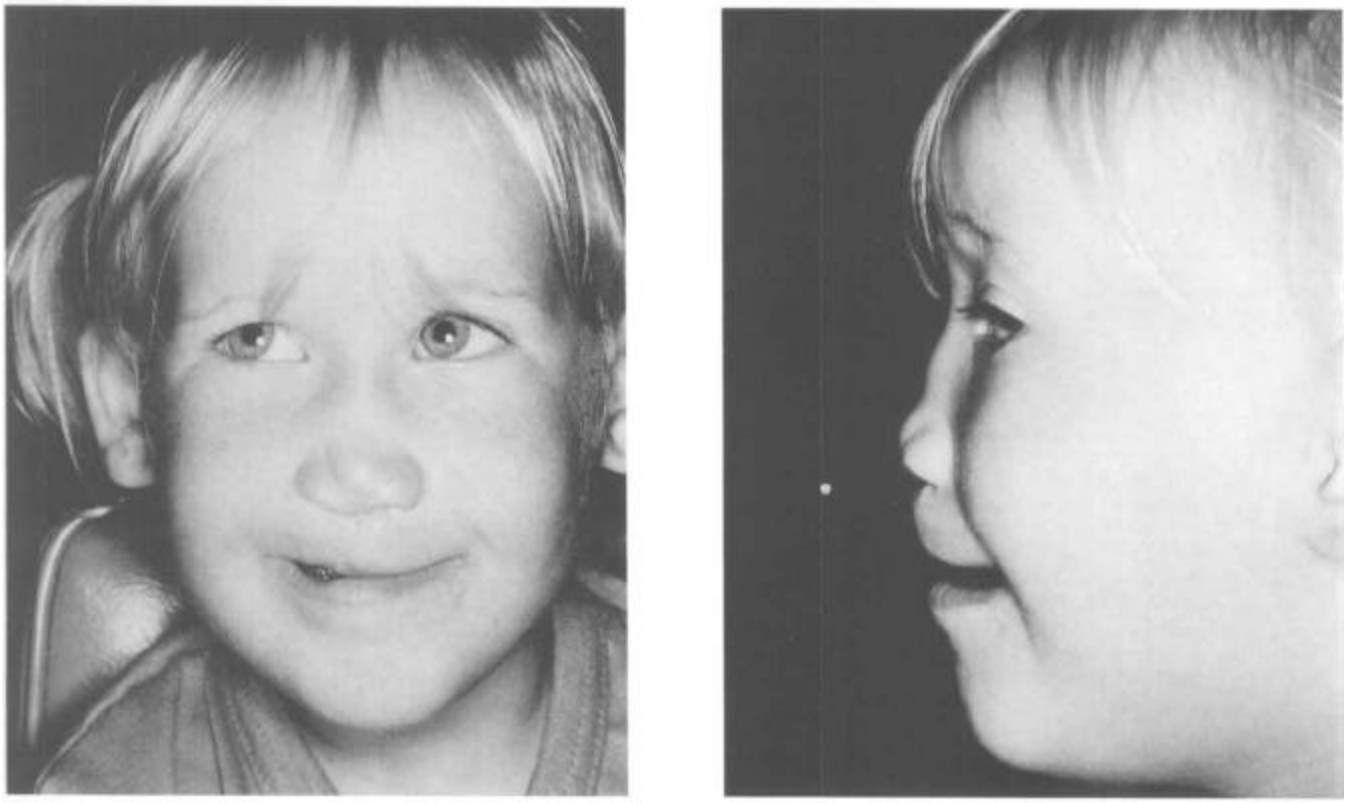


FIGURE 2 Case 1 at 3 years, 4 months of age.

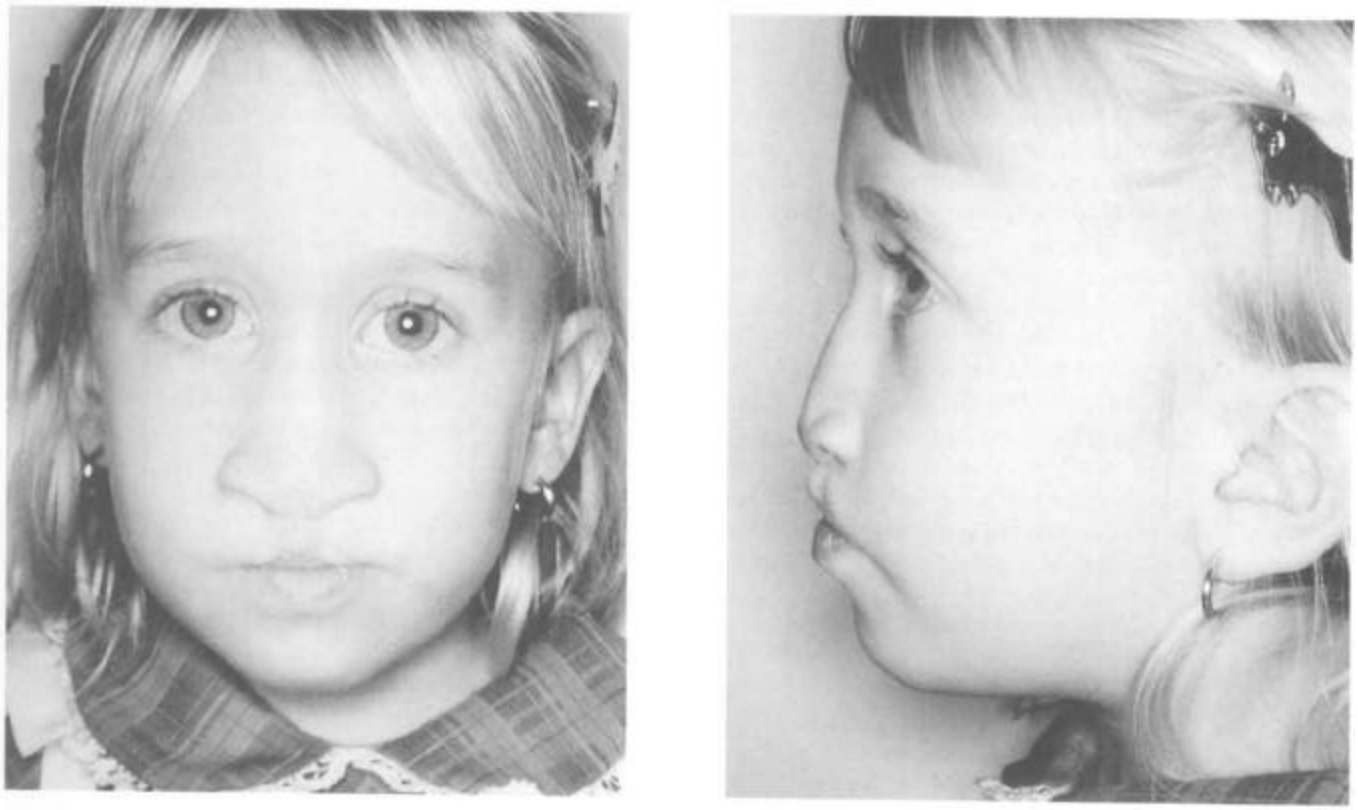


FIGURE 3 Case 2 at 3 years, 7 months of age.

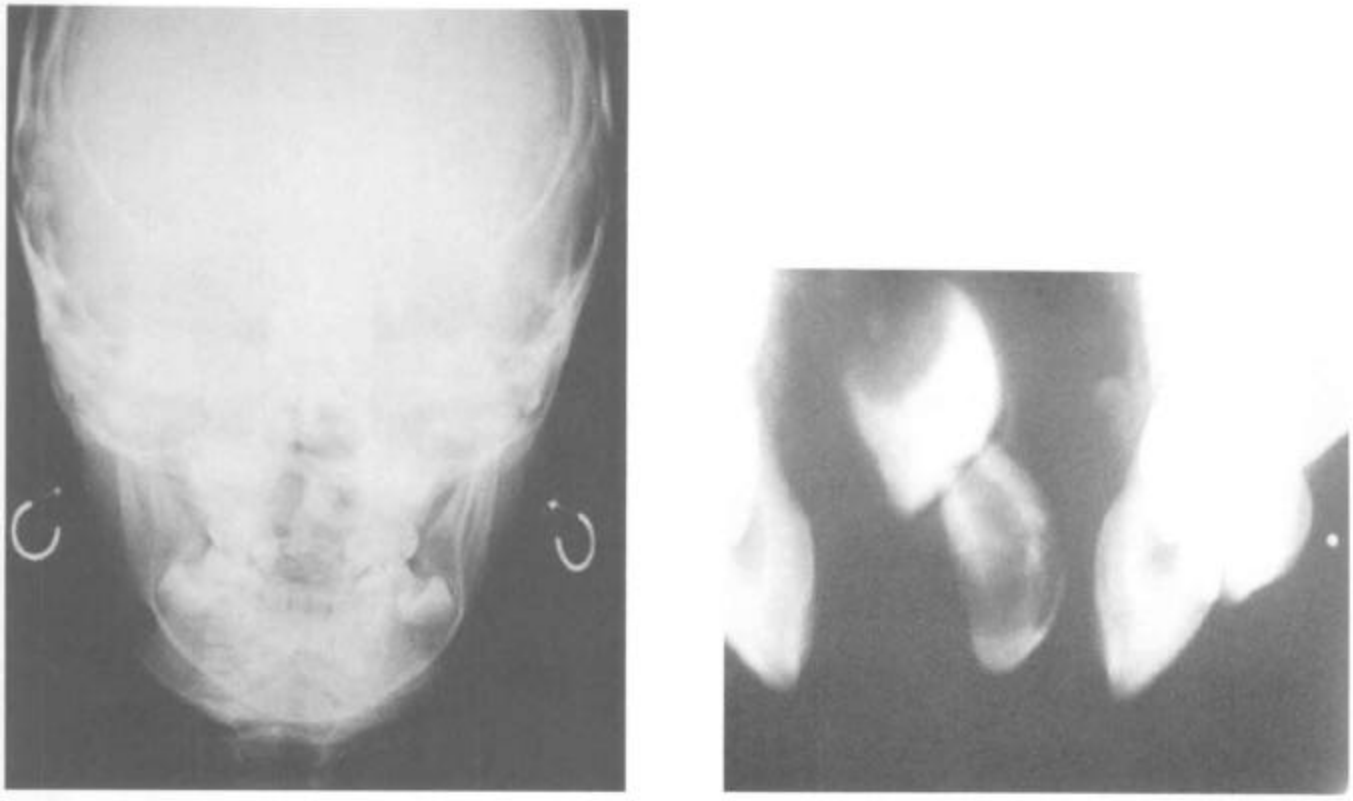
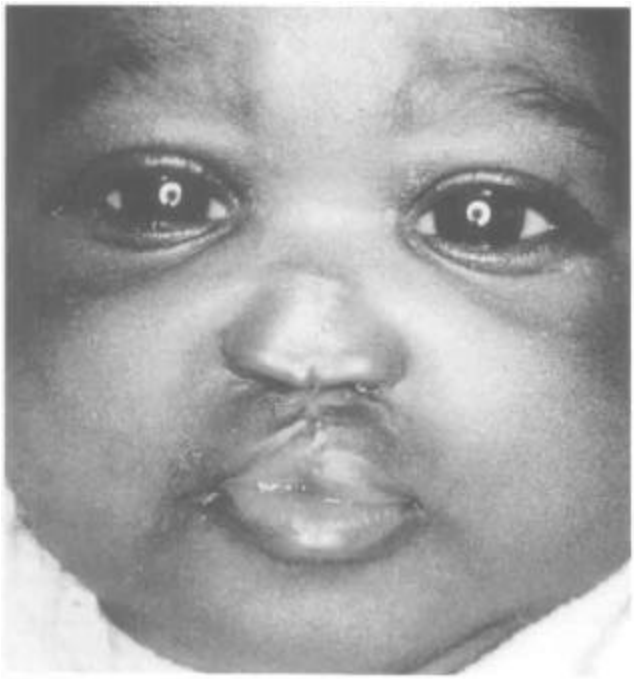


FIGURE 4 Anteroposterior cephalogram (*left*) and occlusal x-ray of single central incisor (*right*) in Case 2 at 3 years, 7 months of age.



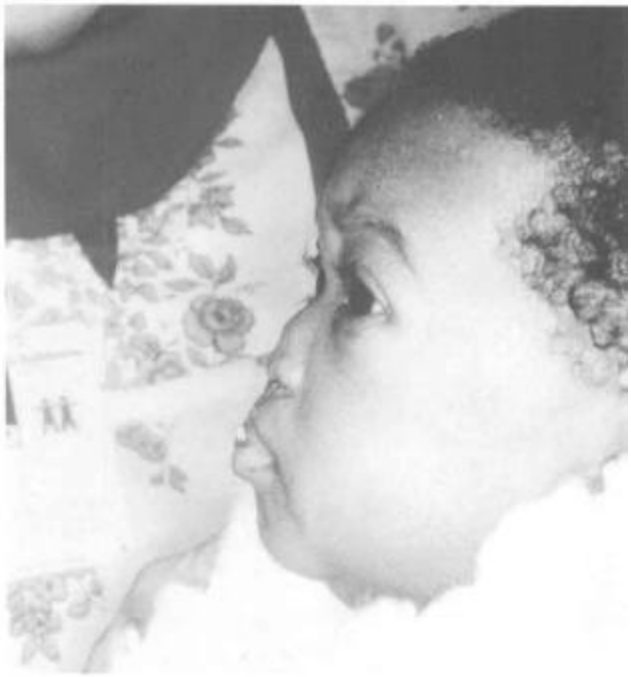


FIGURE 5 Case 3 at 3 months of age.

Height and weight were at the 5th percentile. A wrist radiograph done at 4 years, 4 months indicated a bone age of 3 years. Head circumference was below the 3rd centile. Growth hormone studies were normal, and an endocrine diagnosis of constitutional short stature was given.

Cognitive function was evaluated at 4 years, 10 months of age (Stanford Binet Intelligence Scale, Form L-M) and an intelligence quotient of 72 was recorded placing her in the borderline range of intellectual functioning. Smell was reported to be functional.

Case 4

This 4 pound, 5 ounce black female (Fig. 6) was born 2 months prematurely by spontaneous vaginal delivery to a 34-year-old gravida 2, para 2 mother and a 42-year-old father. There was no known family history of facial clefting. Mother was a borderline diabetic with kidney problems and high blood pressure. She dieted and lost 30 pounds during the gestation. There were two normal male siblings, 12 and 15 years of age.

The baby was incubated after birth for temperature control. Feeding was difficult. She required a blood transfusion at 3 to 4 weeks for anemia. After 1 month her weight was 5 pounds. Her cleft lip was repaired at 2 months of age. The surgeon reported a bilateral cleft palate with median cleft lip, agenesis of the philtrum, with the base of the columella attached to the right maxilla and almost transversely oriented to the right side. The premaxilla amd vomeroseptal structures were absent. The nose was very flat and unsupported (Fig. 6).

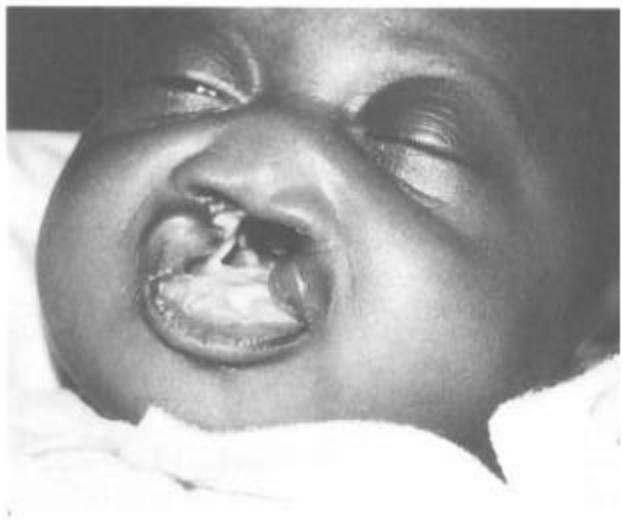


FIGURE 6 Case 4 at 6 weeks of age.

Physical examination at age 5 1/2 months showed an infant who was alert and playful with a small head volume, repaired cleft lip, and prominent ears (Fig. 7). Head circumference, body height, and body weight were well below the 2nd centile. Increased muscle tone in the lower extremities was noted.

Myoclonic seizures developed by 1 year of age, marked by jerking of the upper extremities. Height, weight, and head circumference were below the 2nd centile. The Denver Development Screening Test revealed markedly delayed

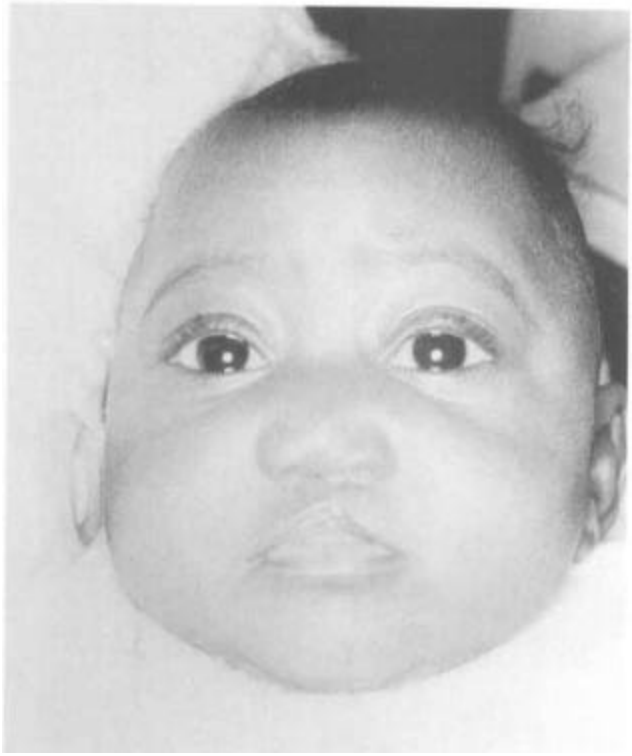


FIGURE 7 Case 4 at 5 months of age.

development of all parameters. Neurologic examination showed very mild spasticity in all extremities and inability to follow objects visually, but the pupillary response to light was present in both eyes. X-ray examination of the chest did not show any abnormalities.

At 3 years of age, cerebral palsy and mental retardation were evident. Seizures continued, partially controlled by Clonazepam. Sonograms of the kidneys, liver, and gall bladder were normal. Height, weight, and head circumference were below the 2nd centile.

At 4 years of age, intraoral examination showed a Class I buccal segment relationship. Cephalometric examinations showed a Class III facial type with premaxillary agenesis and normal maxillary width. Cephalometric study at 48 months of age showed an interorbital distance nearly 2 SD below the mean (Ishiguro et al, 1976). SN (42.3 mm) was 72 percent of the normal (58.7 mm); the sphenoid (13.5 mm) was 59 percent of normal (23 mm), and the ethmoid (22.5 mm) was 79 percent of normal (28.5 mm) (Broadbent et al, 1976). A CT scan with multiple axial views and coronal reconstruction was done and showed frontal atrophy and a slight spreading of the frontal horns. The anterior aspect of the falx was present. No karyotype, no growth hormone studies, or ophthalmologic evaluation was done.

She has had recurrent otitis media with effusion, adhesions, granulation, and recurrent cholesteatoma of the left ear. Cognitive assessment was not requested because she had been assessed by the school system and found to be severely multiply impaired, which included severe cognitive deficiency.

Case 5

This 6 pound, 15 ounce black male was born to a 36-year-old male and 35-year-old, grava 2, para 2 female who was on medications for high blood pressure throughout pregnancy and on insulin for diabetes with onset in the eighth month of gestation. The mother also had a history of psychotic episodes for which she had been treated. Microcephaly and vomeroseptal, premaxilla, columella, and prolabium agenesis were present (Fig. 8) with clefting of the secondary palate and bilateral anotia. There was no known family history of craniofacial malformations.

He was hospitalized at 6 months of age for a cyanotic episode, suspected gastroesophageal reflux, and failure to thrive. An EEG at that time was markedly abnormal, indicative of an encephalopathic epileptic disorder. A CT scan of the head indicated prominent lateral ventricles, especially in the body and occipital horns. There was also minimal cortical atrophy in the frontal lobes (Fig. 9). Significant developmental delay was documented at that time and skull radiographs indicated hypotelorism. He was admitted to the hospital on multiple occasions for failure to thrive, seizures, apnea, and dehydration. Height and weight have continued to be below the 2nd centile. He was found to have diabetes insipidus and incomplete colonic emptying. Lower segment Hirschsprung's aganglionic megacolon could not be ruled out. A gastrointestinal tube was placed at 20 months of age. A CT scan of the cranium done at 16 months of age revealed ventricular deformity with absent septum pellucidum consistent with dysgenesis of the corpus callosum along with lobar holoprosencephaly (Fig. 9).

Cephalometric study at age 10 months (Fig. 10) showed an interorbital distance 44.4 percent of normal (Ishiguro et al, 1976). SN (40.5 mm) was 5 SD below the mean (Friede et al, 1986). The sphenoid (13.3 mm) was 65 percent of normal (20.4), and the ethmoid (20.7 mm) had the least reduction at 82 percent of the norm (25.4 mm) (Broadbent et al, 1976).

A bilateral hearing impairment, at least in part conductive in nature, consistent with atresia of the external auditory canals (documented by CT scan of the temporal bones) was identified. He was given a bone conduction hearing aid. Language and speech development were essentially nonexistent. Developmental delay was considered to be very severe. Bone age studies done at 18 months of age were consistent with a male child of 3 to 6 months of age. There was bilateral coxa valga. Ophthalmologic evaluation revealed an asymmetric eye blink and left exotropia and hyperopia.

Discussion

Ben Hur et al (1978) reported that median facial deficiencies do not have clear nosologic categories. If all of our cases had

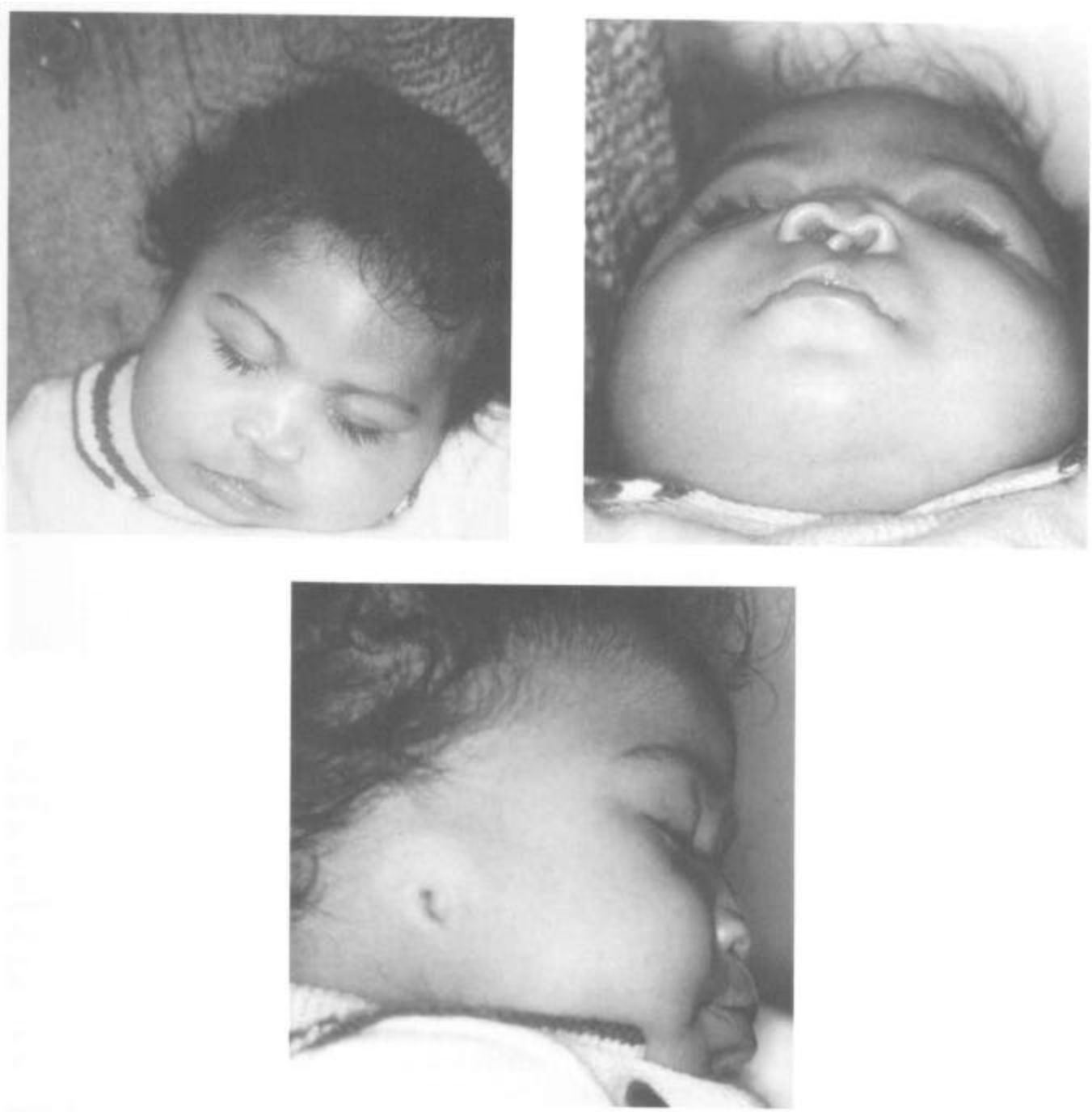


FIGURE 8 Case 5. Full face view shows hypotelorism (*top*). Submentovertical view (*right*) shows residual nasal deformity with deficiency of the nasal septal strut and columella well after lip repair. Lateral view (*bottom*) shows right side of bilateral anotia.

had ethmoid, nasal bone, and midline cerebral dysgenesis, then they would clearly fall under the classification of holoprosencephaly sequence (DeMyer et al, 1964), the recently proposed category of midline prosencephalic dysgenesis (Leech and Shuman, 1986), or interophthalmic dysplasia of the embryologic classification (van der Meulen et al, 1983). A differential diagnosis based on the presence or absence of ethmoid, nasal, crista galli bony dysgenesis, and midline cerebral dysgenesis is logical and important for nosologic, clinical, and research reasons.

Midline prosencephalic dysgenesis was found in one of the three cases studied with CT. The other two patients who were not surveyed had normal intellectual functioning. Although midline cerebral dysgenesis cannot be ruled out, agenesis of

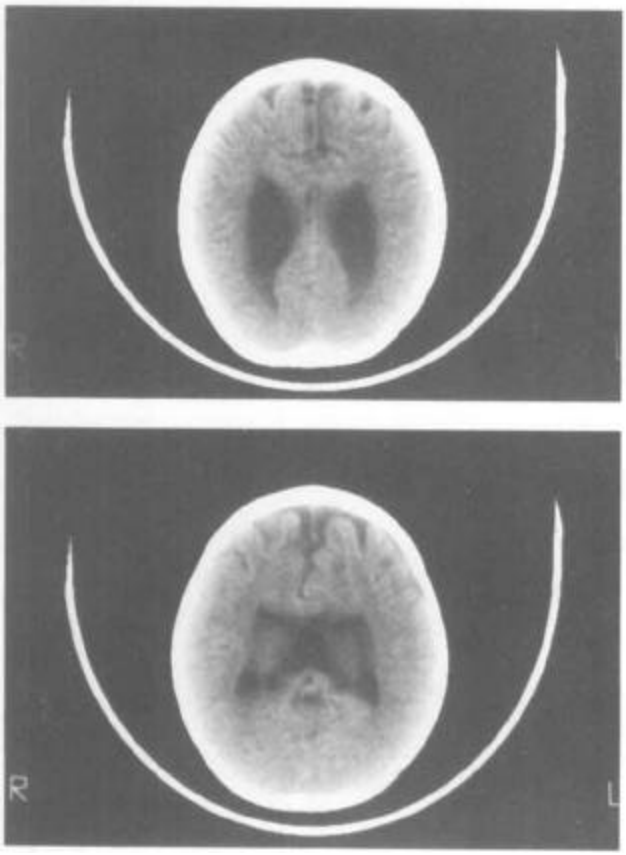


FIGURE 9 CT shows the brain anomaly including enlarged ventricules (*top*) and lobar holoprosencephaly (*bottom*).

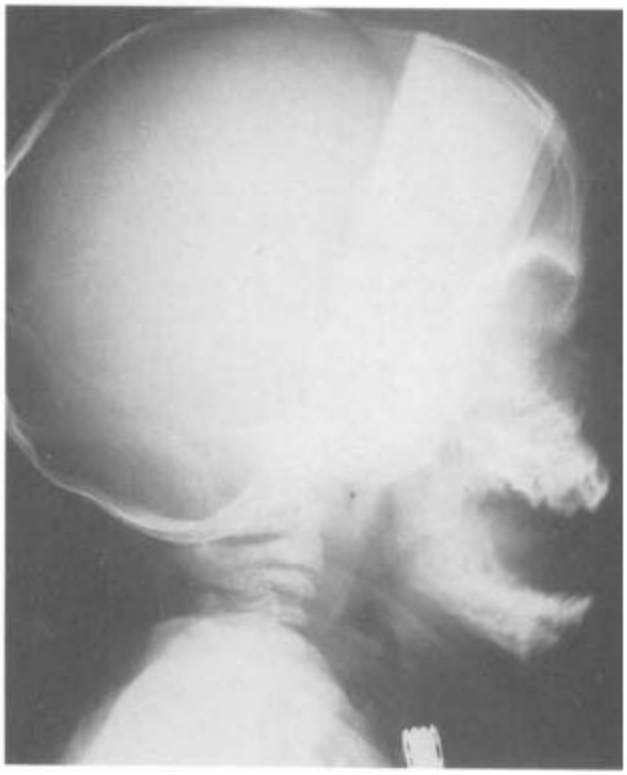


FIGURE 10 Lateral cephalogram of Case 5.

the ethmoid, crista galli, and nasal bones was not found in any of our subjects. This pattern of craniofacial dysplasia should be clearly implied in the label "interophthalmic dysplasia" or "DeMyer sequence."

Two of our cases (4 and 5) had diabetic mothers. These two cases are similar to the ones reported by Barr et al (1983) who indicated that holoprosencephaly is a possible risk for children of diabetic mothers.

In our five reported cases and in the one by Pashayan and Lewis (1980), no association with immediate family history for facial clefting or dysmorphia was found, though one of our cases had a maternal cousin with cleft palate. Other reports show the absence of a positive family history for median facial dysmorphia with oral cleft and pituitary dysfunction (Laron et al, 1969; Zuppinger et al, 1971) and with single central incisor cases (Fulstow, 1968; Holm and Lundberg, 1972; Rappaport et al, 1977; Wesley et al, 1978). A majority of reported cases with various forms of median facial agenesis have no known family history of facial malformation.

A positive family history for holoprosencephaly or DeMyer sequence has been reported in eleven instances (Grebe, 1944; Kopp, 1967; Dallaire et al, 1971; Patel et al, 1972; Lowry, 1974; Roach et al, 1975; Martin et al, 1977; Cantu et al, 1978; Benke and Cohen, 1983; Berry et al, 1984; Ardinger and Bartley, 1988). Kopp (1967) reported a mother and daughter of normal stature with single central incisors. Lowry (1974) reported a mother with a single central incisor, normal stature, and hypotelorism having an offspring with holoprosencephaly sequence. These cases suggest an autosomal dominant mode of inheritance when a positive family history is found. It was suggested by Ardinger and Bartley (1988) that when any signs of the DeMyer sequence are found, evaluation of relatives for minimal signs should be made, such as hypotelorism, central incisor agenesis, and especially head circumference. Reduced head circumference was found to be the best indication of a Mendelian pattern of inheritance.

In case reports, Pashayan and Lewis (1980) reported stature at the 3rd centile for length and 10th centile for weight. Ben Hur et al (1978) did not report on stature. Body stature in the cases presented here ranged from 2nd to 10th centiles. Small body stature and median facial structural agenesis apparently occur together more frequently than by chance. This association can be seen in cases with a single central incisor as the only clinical expression of midline agenesis (Fulstow, 1968; Rappaport et al, 1976, 1977) with two of the studies reporting growth hormone deficiency (Rappaport et al, 1976, 1977). Short stature, solitary central incisor, and normal growth hormone assays have been reported (Rappaport et al, 1976,

1977). Growth hormone and somatomedin assays were also normal in the three cases tested and herein presented. On the other hand, normal stature and single central incisor phenotype have been reported (Scott, 1958; Kopp, 1967; Lowry, 1974; Holm and Lundberg, 1972; Wesley et al, 1978).

Short stature and growth hormone deficiency have also been associated with cleft lip and palate (Laron et al, 1969; Zuppinger et al, 1971) with choroidal coloboma (Zuppinger et al, 1971), and with septo-optic dysplasia (Hoyt et al, 1970). Furthermore, short stature can be affiliated with a spectrum of associated median nonfacial defects such as in the VATER association (Quan and Smith, 1973). Gareis and Smith (1971) reported a case with short stature, cleft palate, normal laboratory tests, and 10 similar cases among siblings and relatives.

Pashayan and Lewis (1980) reported a single case with vomeroseptal and crista galli agenesis (ascertained from frontal cephalogram), prolabium hypoplasia, premaxillary hemigenesis with fused single left central and lateral incisors, and complete cleft lip and palate. Ben Hur et al (1978) reported columella, nasal skeleton, and premaxilla agenesis without clefting of the secondary palate. The clefting of the secondary palate is perhaps overlaid on this kind of dysplasia, since both may share a common causality (tissue deficiency) but are specifically heterogeneous.

In case 2 the retracted position of the premaxilla probably reflects the loss of the proposed vomeroseptal "morphogenetic template" (Burdi, 1976) and "distusion field" (Blechschmidt, 1976) in embryogenesis.

Median facial structural agenesis including the premaxilla may be associated with or without clefting of the secondary palate, or as a less severe expression when a partial premaxilla is present as in case 2 and also reported by Pashayan and Lewis (1980), and Frances et al (1966), or when the only agenic structure is a central incisor (Rappaport et al, 1977; Wesley et al, 1978).

Intellectual function and developmental milestones may be normal, but microcephaly (Cases 4 and 5), midline prosencephalic dysgenesis (Case 5), and low I.Q. (Case 3) may be found. One case reported by Rappaport et al (1977) had a low I.Q. and a case reported by Fulstow (1968) had microcephaly. Interestingly, both of these cases had only single central incisor. Causally related factors associated with an alcoholic mother (Case 3) and a diabetic mother (Cases 4 and 5) may explain in part the heterogeneity of brain dysfunction and its sporadic association with the dysplasia in the cases presented.

For four of the cases reported in this paper, interorbital distance was not predictive of intellect, showing an inverse relationship to IQ scores. However, when the size of the anterior cranial base was related to intelligent quotient, a positive relationship was seen. Of course, the sample size is too small for general conclusions to be drawn.

The anterior cranial base in all subjects was short. A reduced sphenoid component (S-Se) and a relatively larger or normal ethmoid component (Se-Eth) were found in all subjects.

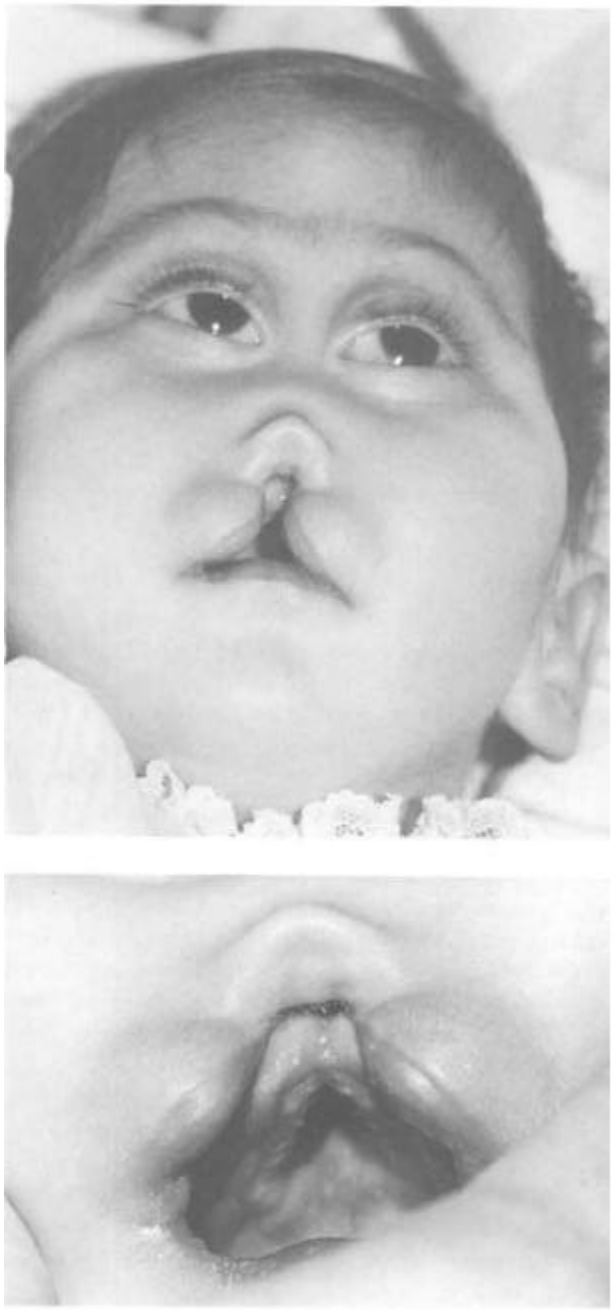


FIGURE 11 Patient with hypotelorism, nasal hypoplasia, and premaxilla, prolabium, columella, and septum aplasia (*top*) with intact secondary palate (*bottom*).

The potential significance of the relatively normal ethmoid size in the reported cases should be noted. In cases of cyclopia, ethmocephaly, and cebocephaly, the ethmoid complex is usually agenic, and major brain malformation is seen as an undivided prosencephalon (DeMyer et al, 1964; Cohen et al, 1971; Rowlatt and Pruzansky, 1980; Bacon and Remy, 1983). It may be hypothesized that in all cases with both alobar holoprosencephaly and midline facial stigmata the

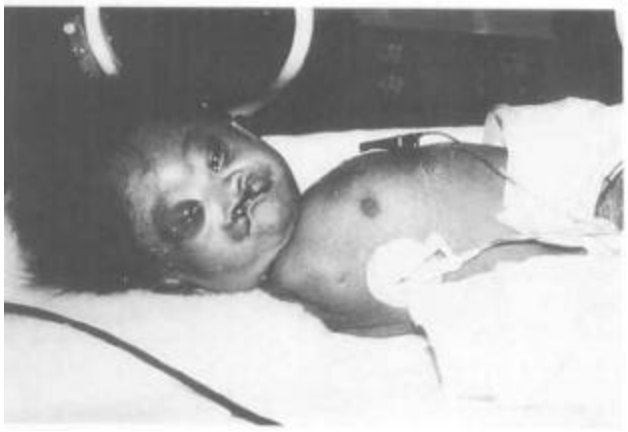


FIGURE 12 Patient with anencephaly, hydrocephaly, microphthalmia, unilateral cleft lip and palate, and median facial structural competence without hypotelorism.

ethmoid complex will be wholly or partially aplastic. Therefore there may be an obligate developmental relationship between midline face and brain dysmorphia to the extent that the ethmoid complex is primarily involved. Petterson (1976) has postulated that the ethmoid bone is the key to the midfacial defects, and the prosencephalon is the key to the intracranial defects. However, the ethmoid, when malformed, may be the key to both defects in such cases.

A case example of holoprosencephaly sequence with hypotelorism, absent nasal bones, and deficient ethmoid bone with absence of the crista galli is illustrated by Cohen and Hohl (1976, p. 395). Another one of our patients, without clefting of the secondary palate, had agenesis of the nasal bone, ethmoid, vomeroseptal complex, and premaxilla with alobar holoprosencephaly and severe hypotelorism (Fig. 11).

However, Figure 12 shows a case of ours with unilateral cleft lip and palate with intact median facial and cranial base structures, microphthalmia, hydrocephaly, and alobar holoprosencephaly without hypotelorism. In one instance, facial dysmorphia reflects a major brain malformation, but in the other no median facial criteria relates to an equivalent brain malformation.

When the face and brain are related by dysmorphia, the ethmoid has a major involvement as cited by Cohen and Hohl (1976) and Petterson (1976). However, a major brain malformation may exist without affecting the ethmoid and without predictive midline facial or orbital position stigmata. Other factors may cause a face to appear similar to one where the ethmoid and nasal bones are affected (Pashayan and Lewis, 1980; Ben Hur et al, 1978) where the ethmoid and nasal bones are intact. However, in these cases, midline facial dysgenesis is not likely to be pathognomonic for midline prosencephalic dysgenesis.

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Commentary

The interesting paper by Spolyar et al underscores two important points. The first is the growing tendency for clinicians to rely more heavily on radiologic imaging studies of the brain. The authors describe five children, all of whom had craniofacial features consistent with the so-called holoprosencephaly malformation sequence. Growth and development were completely normal in two of these patients while the remaining three children had evidence of growth failure and developmental delay. CT scans were not performed in the two children who were developmentally normal, and, of the three patients in whom CT scans were performed, only one (patient 5) was found to have clear evidence of midline defects of the brain. The conclusion one reaches from reviewing these cases is that in contrast to DeMyer's hypothesis, the face does not necessarily predict the brain.

In our experience, however, this view is not correct. Over the past few years, we have evaluated 5 children with craniofacial defects suggestive of the holoprosencephaly malformation sequence (including 4 with midline cleft of the lip and palate, 3 with ocular hypotelorism, and 3 with hypoplasia of the nose) in whom CT imaging of the brain failed to reveal an associated cerebral malformation (Motzkin et al, 1990). Like some of the patients described by Spolyar et al, developmental disability, growth failure, and other medical complications possibly related to pituitary dysfunction were found in our patients. Although CT scans in every case were interpreted by neuroradiologists as being normal, further evaluation of the brain, either through postmortem studies or MRI, revealed the presence of midline defects ranging from isolated absence of the hypothalamus and pituitary to lobar holoprosencephaly with arrhinencephaly. To summarize these findings, our experience suggests that not only does the face predict the brain, but it also is a better predictor than the CT scanner!

This message is far from trivial. The management of patients with clefts or craniofacial anomalies who have midline brain defects must be significantly different from that of individuals in whom the brain is judged to be normal. For example,

growth hormone deficiency, hypothyroidism, and other endocrinologic disorders related to defects in pituitary function must be actively pursued in the former group of patients, and institution of treatment for such problems, if undertaken early in life, may lead to a far better outcome.

The second important point made by this paper is that the term "DeMyer sequence," first proposed by Jaramillo et al in 1988, is more appropriate than the previously used "holoprosencephaly malformation sequence." To some physicians, holoprosencephaly has a narrow, specific meaning. In this sequence, however, the malformations that occur in the brain cover a wide spectrum unified by the fact that they involve the midline. Thus, to avoid misunderstanding among medical professionals from different specialties, the term "DeMyer sequence," although less descriptive, is probably a better choice.

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