1 Facial clefts and associated limb anomalies: description of 3 cases and a review of the
2 literature

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37 Abstract

38 Facial clefts are rare congenital malformations. In the literature these are sometimes
39 reported in combination with limb malformations, especially ring constrictions. This
40 article describes 3 cases of children with facial clefts and limb ring constrictions with
41 various expressions. The first case has a lateral cleft with associated limb malformations.
42 This combination has, to our knowledge, not yet been reported. The literature about facial
43 clefting and the amniotic band syndrome and the possible aetiology of clefting and
44 constrictions in these cases are discussed.

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46 Key words: Facial cleft, limb malformations, etiology, Tessier, Amnion band

INTRODUCTION

Facial clefts, as clearly classified by Tessier (1976), are rare congenital malformations with an unknown etiology. They have been reported in association with other congenital malformations, particularly of the extremities. Especially limb constriction bands and amputations are consistently noted. Amniotic band syndrome has been associated with these malformations, but the exact mechanisms causing this condition are unclear. Proposed theories include interruption of fetal blood supply, genetic programming errors, defects of embryological organization and mechanical deformation by amniotic bands.

We present 3 patients with facial clefts and limb malformations as described in amniotic band syndrome, treated in Groningen (The Netherlands) and Gent (Belgium). We also discuss the possible etiology by reviewing the literature. By presenting these cases we would like to add new examples of patients with a combination of malformations considered to be part of the amniotic band syndrome.

CASE-REPORTS

Patient 1

A 6 months old girl was presented to our outpatient clinic with a bilateral facial cleft and limb malformations. She was the first child of nonconsanguineous parents of Afro-Caribbean origin, born after a regular pregnancy and delivered by means of a Caesarian section. There were no visible anomalies of the placenta. Her mother suffered non-insulin dependent diabetes and hypertension during her pregnancy. The family history was negative for craniofacial or other congenital malformations. The mothers' sister had sickle cell anemia but blood samples of the child were normal.

On clinical examination multiple congenital malformations were seen (Fig 1,2):

- Oblique cleft through her left and right cheek
- Constriction band around her right upper arm
- Skin tag on the back of her head

Syndactyly of the 2nd, 3rd and 4th toe of the right foot
Flexion contracture and hypoplasia of the right great toe
At neurological examination she had normal reflexes and a normal movement pattern.
Chromosomal analysis of the blood samples showed a normal female karyotype (46,XX).
A MRI and CT scan were performed which showed a cartilaginous tumor in the right
maxilla with tooth follicles.
She was operated and the left hemifacial cleft was closed, the constriction band on her
right arm was interrupted with Z-plasties and the skin tag on the back of her head was
excised. The maxillary tumor was excised and the right hemifacial cleft was closed. The
operation was without complications and post-operative healing was uneventful.
Histological examination of the maxillary tumor showed no indications for malignant
cells.
The patient was seen again in the outpatient clinic 1 year after surgery. The wounds had
healed without hypertrophic scarring. Her facial expression was normal. There were no
signs of recurrence of the maxillary tumor.

Patient 2

A newborn baby boy was transferred to our clinic because of multiple congenital
malformations. He was the first child of nonconsanguineous Caucasian parents, born by
means of a Caesarean section after a pregnancy of 36 weeks, during which
oligohydramnios was noted. On examination of the placenta, strands and villiform
appendages were seen at the umbilical cord and the fetal side of the placenta. The family
history was negative for craniofacial or other congenital malformations.
On clinical examination multiple congenital malformations were seen (Fig 3,4,5,6):
Skin tag on the right forehead
Coloboma of the left iris, combined with a chorioretinal and optic nerve coloboma

Bizarre shape of the nose with a notch of the right ala and a sinus tract in the left nostril

Slight hypertelorism with asymmetric eyebrows

Bilateral choanal atresia

Narrow, high arched palate with a bifid uvula

Constriction bands on the right upper and lower leg with a small skin tag on the ventral side of the lower leg

Syndactyly of the 2nd, 3rd and 4th finger of the left hand with amputation on the level of the PIP joint

Amputation of the 2nd, 3rd and 4th finger on the level of the DIP joint of the right hand, with constriction rings proximal

Amputation of the toes of the left foot on the level of the PIP joint

There were no abnormalities of the internal organs. Blood samples were normal and genetic examination showed a normal 46 XY karyotype. CHARGE association was excluded as the boy presented with only two of the six malformations described in the CHARGE association (Pagon et al 1981). During his first year he underwent several surgical corrections, during which the skin tag was removed, the constriction bands on the leg were corrected with multiple Z-plasties and the syndactylies of the left hand were corrected. The pathology report of the skin tag showed normal skin and subcutaneous tissues. Surgery and postoperative healing were uneventful.

He was followed in the craniofacial team of the UZ Gent and developed normally. At the age of 11 years, the choanal atresia was corrected. For further surgical planning, a CT scan was performed with 3D reconstruction at the age of 14, which revealed a bony cleft on the right side of the nasal bone. Because of the high arched palate and occlusional problems, distraction of the palate with orthodontic treatment was started. A nasal correction was also performed and further corrections are planned in the future.

Patient 3

A newborn baby boy was referred to our clinic because of multiple congenital

malformations. He was the first child of nonconsanguineous parents of Mediterranean origin, born after a pregnancy of 38 weeks, during which the mother had hypertension. Examination of the placenta showed an umbilical cord with velamentous insertion. The family history was negative for craniofacial or other congenital malformations. On clinical examination multiple congenital malformations were seen (Fig. 7,8,9,10):

- Parietal encephalocele with brachycephaly based on right sided coronal suture stenosis
- Bilateral asymmetric cleft lip and palate
- Slight hypertelorism with asymmetric eyebrows
- Retrusion of the right orbital region
- Syndactyly with amputation of 2nd, 3rd, 4th and 5th finger of the left hand
- Syndactyly with amputation of all fingers of the right hand
- Amputation with syndactyly of 2nd and 3rd toe and constriction rings of the 4th and 5th toe of the right foot with amputations
- Syndactyly of the 2nd and 3rd webspace of the left foot, amputation of 2nd, 4th and 5th toe
- Skin tag in the lumbal area

During the first two years of life, several corrections were performed of the cleft lip and palate, hands and feet and encephalocele. The pathology report of the excised skin tag showed normal skin and subcutaneous tissues. An epidermoid cyst was found close to the encephalocele. The boy also suffered from epileptic seizures, controlled by anti-epileptic medication. A CT-scan revealed multiple deformities on the right side of the brain (ventricular deformities, lobar holoprosencephaly, kissing thalami).

No other abnormalities of the internal organs were discovered. Genetic examination was not performed as the parents refused this.

The boy was followed for 12 years in the craniofacial team, further surgical corrections were scheduled but unfortunately the boy was then lost to follow-up.

DISCUSSION

The amniotic band syndrome or amniotic disruption sequence is a constellation of congenital malformations characterized by extreme variability. These include limb reductions, craniofacial malformations, body wall deficiencies, clubfeet and internal organ anomalies (Patterson, 1961; Bamforth, 1992; Froster and Baird, 1993; Van der Meulen, 1999; Goncalves and Jeanty, 1999). It is also mentioned under the name of ADAM sequence (amniotic deformity, adhesions, mutilations) which is identified in the study of Yang (1990) as being a complication of EAR (early amnion rupture).

Our patients presented with a combination of facial clefts and limb deformities, which clinically seemed to fit in the amniotic band syndrome.

Similar malformations have been numerous reported (Sakurai et al., 1966; Jones et al., 1974; Mayou and Fenton., 1981; Garza et al., 1988; Coady et al., 1998; Van der Meulen, 1999; Kara and Ocsel, 2001; Gokrem et al., 2002; Morovic et al, 2004).

In 1998 Coady et al (1998) wrote an extensive report on their population of patients with facial clefts. They found 11 patients with facial clefts and limb deformities, consisting of ring constrictions. All facial clefts were in the central axis of the face and they suggested an association between rare craniofacial clefts and limb ring constrictions and postulated a common etiology.

In a case-report by Kara et al. (2001), a patient was described with a Tessier no 5 cleft with extremity malformations (multiple random-pattern asymmetric extremity deformities). In Gökrem's group of 5 patients with a Tessier no 7 cleft, none of the patients had associated limb malformations (Gokrem et al, 2002). Our patient with the lateral cleft (patient 1) had limb malformations and as far as we are aware, this would be the first case reported in the literature.

Jones et al (1974) and Morovic et al (2004) published a series of patients with craniofacial and extremity malformations comparable to the malformations of our patients. They assumed the malformations were due to amniotic bands as a result of early amniotic rupture.

Tessier (1976) published an article on the classification of facial, craniofacial and laterofacial clefts. The purpose of his article was to propose a descriptive classification of

the clefts, based on the clinical findings, but did not explain the etiology. Van der Meulen et al. (1983) proposed a classification based on morphogenetic characteristics. They introduced the term “dysplasia” and described the malformations according to the localization and timing of developmental arrest based on the embryology. David et al. (1989) added a third dimension to the Tessier classification by describing the anomalies found on CT scans and three-dimensional reconstruction.

Little is written about the epidemiology of rare facial clefts or the distribution among races. In a review by Kawamoto (1976), facial clefting has been reported in 1.43 to 4.85 in 100,000 births. The Tessier no. 7 cleft is the least rare atypical craniofacial cleft with an incidence from 1:3000 to 1:5642 live births, but bilateral involvement is rare (Tessier, 1976).

Concerning the epidemiology of amnion rupture defects, Garza et al. (1988) indicated that the incidence is around 1.16 per 10,000 live births. It occurs 1.76 times more often in blacks and especially young black nulligravidas have a significant higher risk of having a baby with amniotic band syndrome anomalies.

The mothers of two of our patients had hypertension during pregnancy but we did not find suggestions in the literature that this could be a risk factor for the development of amniotic bands. Oligohydramnios was noted during the pregnancy of patient 2 and this has been associated with compression-related malformations of the craniofacial area and limbs (Torpin, 1968; Marino, 2004).

The etiopathology of facial clefting has been hotly debated for centuries. It has been considered as a failure of fusion of primordial facial processes as described by Dursy in 1869 and His in 1892 (Classic Theory). Later Warbrick (1963) and Stark (1954) described their theory of a failure of migration of mesoderm and neural crest (Modern theory).

Multiple theories have arisen around the etiology of the amniotic band syndrome.

The intrinsic theory considers focal fetal dysplasias to be the cause of the constrictions (Streeter, 1930). Patterson proposed diagnostic clinical criteria for the diagnosis limb ring constrictions often seen in the amniotic band syndrome:

221 1. Simple ring constrictions

222 2. Ring constrictions with distal deformity plus or minus lymphedema

223 3. Ring constrictions accompanied by syndactyly or acrodactyly

224 4. Amputation

225 After an extensive search of the literature, Patterson (1961) concluded that the underlying
226 cause is a failure of development similar to that of other congenital malformations

227 The malformations are the result of developmental errors in the formation of connective
228 tissue, resulting in facial clefts and limb malformations. Different mechanisms have been
229 suggested including vascular failure with disruption of epiblastic cells, disturbance of
230 neural crest cell migration etc., with secondary limb amputations, constriction bands,
231 cephaloceles, syndactyly, clubfeet, club hands and internal anomalies (Lookwood et al.,
232 1989; Bamforth, 1992). In 1986 Hunter and Carpenter discussed in their paper four
233 infants with ABS and additional malformations that were not readily explainable on the
234 basis of band disruptions. Their conclusion was that some extrinsic insult or perhaps
235 occasionally a familial susceptibility leads to loss of fetal vascular integrity, superficial
236 hemorrhage and denudation, with adhesions leading to syndactyly, and constrictions to
237 amputations (Hunter and Carpenter, 1986).

238 The extrinsic theory claims that the bands cause the clefts and limb constrictions.
239 Rupture of the amnion would lead to bands or strands that entangle body parts of the
240 fetus, and swallowing of the strands leads to clefts in the face (Patterson, 1961). In one
241 series, a histologically proven amniotic band was found (Mayou and Fenton, 1981). The
242 problem with the extrinsic theory however is that bands have never been observed in
243 natural creases below the nose or behind the ear. Furthermore bands cannot explain the
244 typical pattern of clefts, cannot produce perfectly symmetric clefts and related anomalies
245 (Van der Meulen, 1999).

246 A third theory assumes that these malformations are part of the amniotic rupture
247 syndrome together with disruptive defects. The resulting oligohydramnios would induce
248 compression related deformities. The earlier the rupture and the more susceptible the
249 developing areas, the more severe the defects including craniofacial malformations, limb

anomalies and visceral defects (Higginbottom et al., 1979; Van der Meulen, 1985; Morovic et al., 2004).

But even with all these theories it remains difficult to explain the different malformations in one patient. The debate should probably not be focused on the terminology of the malformation but rather on the mechanism causing the malformation or combination of malformations. The first patient had a bilateral oblique cleft. The third patient had an asymmetric bilateral cleft lip and palate. These are primary clefts, which are formed when fusion between the nasal and maxillary or maxillary and mandibular processes is disturbed before the end of the transformation phase (Van der Meulen et al., 1983). Patient 2 had a secondary bony cleft originating from disturbed ossification of the facial skeleton. Did these developmental disturbances cause the bands, which in turn caused the extremity malformations? Or were the bands a result of amnion rupture, which led to the formation of the facial clefts and strangulation of the limbs?

In our first case, a constriction band could theoretically have caused the facial cleft, although it is difficult to explain the differences in the level of clefting in the right cheek. Constriction bands could certainly have caused the extremity malformations. Furthermore, two articles describe tumors that developed from tissue that was strangled due to an amniotic band (Murata et al., 1992; Tanabe et al., 2002). This phenomenon would account for the tumor that was found in the right maxilla. In the study of Davids et al. (1989) 253 patients were studied but none of the patients had a maxillary tumor like our case, however facial clefts associated with duplication of various oromaxillary components have been reported (Marfeni, 1993) and Converse et al. (1974) found in his series of 280 patients two patients with extramaxillary foci of bone and ectopic dentition. All three patients had a skin tags (back of head, forehead and lumbar region respectively). Ten Donkelaar et al. (2002) described a patient who showed constrictions in both hands and amputations with fresh, healing wounds suggestive for amniotic band syndrome. Their patient also had a skin tag on his head, which after microscopic examination turned out to be rudimentary meningocele with intestinal mucosa probably due to amniotic band syndrome. In patient 1 pathologic examination of the skin tag was not performed but in

patients 2 and 3 the skin tags showed no particular anomalies at histological examination. In the second patient there is clear evidence that there were bands involved as strands and villiform appendages at the edge of the placenta and umbilical cord were found. Oligohydramnios with limited fetal movement was also noted during pregnancy. The strands and oligohydramnios may have caused the extremity malformations, as well as the cleft uvula and high arched palate, due to compression. The facial malformations however are very atypical. Because of the asymmetric face, the notch in the right hemi nose, the right-sided orbital dystopia and the skintag on the right forehead, a bony cleft was suspected, which was confirmed on CT scan. Furthermore, a sinus tract in the left nostril, bilateral choanal atresia, coloboma in the left iris and retina cannot be explained with the extrinsic theory of the amniotic band syndrome and must be due to focal dysplasia.

The third child had a bilateral asymmetric cleft lip and palate but with slight hypertelorism and asymmetric eyebrows, retrusion of the right orbital region and cranial deformities with an encephalocele. His extremity malformations consisting of syndactyly, partial amputations and constriction rings and the skull deformities, consisting of plagiocephaly, synostosis and encephalocele can be produced by compression and therefore could fit into the spectrum of amniotic rupture sequence. Clinical signs of oligohydramnios however were not found during pregnancy.

CONCLUSION

These three cases illustrate that the etiology is probably intrinsic, that the secondary compression is related and that these malformations occur very early in the embryo. The dysplasias in the craniofacial area may have caused amnion rupture, which in turn may have caused the extremity malformations and other compression related deformities. It also seems logic that the earlier the developmental arrest or disturbance takes place, the more severe external malformations will result, as shown in patients 1 and 3. It seems important to continue to collect and publish data on these patients in order to obtain a better understanding of the etiology of this spectrum of malformations.

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Figure Legends

Figure 1: Patient 1, right hemifacial cleft and constriction band on right upper arm

Figure 2: Patient 1, syndactyly of the right foot and flexion contracture of the right hallux

Figure 3: Patient 2, frontal view of the patient with skin tag on the forehead, coloboma of the left iris, bizarre shape of the nose and slight hypertelorism

Figure 4: Patient 2, left hand with syndactyly and partial amputations

Figure 5: Patient 2, right hand with amputations on the level of the DIP joints

Figure 6: Patient 2, constriction band lower extremity

Figure 7: Patient 3: frontal view with bilateral asymmetric cleft lip and palate

Figure 8: Patient 3, lateral view with parietal encephalocele and brachycephaly

Figure 9: Patient 3, left hand with partial amputations of 2nd, 3th, 4th and 5th finger

Figure 10: Patient 3, right hand with partial amputations of all fingers

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