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Classification and phenotypic spectrum of atypical orofacial clefts – A single centre study

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Abstract

Orofacial clefts, among the commonest birth defects, can extend atypically onto splanchnocranium. To analyse the phenotypic spectrum of atypical orofacial clefts and relate clinical diagnosis with other topographic and pathomorphogenetic classifications, a cross sectional descriptive study was performed on 500 children aged ≤18 years with orofacial clefts over three years. Pattern of malformation and clinical diagnosis were established in children with atypical clefts. Evaluation focussed on type of cleft, laterality, dysmorphology and associated anomalies. Topographic and morphogenetic classifications were tabulated against clinical diagnosis. Statistical analysis was descriptive. Results: Among 500 children with orofacial clefts, associated or syndromic clefts were seen in 116 and atypical clefts in 21. Thus, atypical clefts constituted 4.2% of all clefts and 18.1% of associated clefts. Of children with atypical clefts, bilaterality was seen in 11 (52.4%) subjects. Oculo-auriculo-vertebral spectrum constituted the largest group with nine children. Others included Treacher Collins syndrome phenotype, amniotic band sequence, frontonasal dysplasia sequence, holoprosencephaly sequence and heminasal aplasia. A majority were male (16, *i.e.* 76.2%). Risk factors included advanced paternal age, young maternal age and first birth order. Neuroimaging abnormalities included semilobar holoprosencephaly, interrupted ventricular system with schizencephaly and acrania. A majority were lateral clefts corresponding to Tessier 7 (9, *i.e.* 42.9%). Others included oblique (6, *i.e.* 28.6%) and median (6, *i.e.* 28.6%). Morphogenetically, malar and mandibular hypoplasia were significant in nine cases each. In conclusion, atypical orofacial clefts, though rare, constitute an important group of conditions with phenotypic heterogeneity. Topographic and morphogenetic classifications based on different principles would aid in the clinical diagnosis and guide in further work up.

Key words

Amniotic band sequence, associated clefts, lateral clefts, oblique clefts, oculo auriculo vertebral spectrum, pseudoclefts.

Key to abbreviations

ABS	: amniotic band syndrome
FNDS	: frontonasal dysplasia sequence
HPE	: holoprosencephaly
OAVS	: oculo auriculo vertebral spectrum

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OFC : orofacial cleft
TCS : Treacher Collins syndrome

Introduction

A cleft is considered to be a defect in fusion of developmental processes (de Meyer, 1975). Orofacial clefts (OFC) are among the commonest birth defects with a prevalence of 1 in 600 (Mossey and Little, 2009). They contribute to the largest proportion of craniofacial anomalies (Mossey and Castilla, 2001). Other than typical clefts that involve the lip, soft and hard palates, extension atypically onto larger parts of face and cranium can result in heterogeneous phenotypes (Eppley et al., 2005). Atypical clefts contribute to <1% of all OFC and are invariably associated with other anomalies. They are either syndromic or sequences with greater challenges in management (David et al., 1989). Epidemiological studies on OFC generally exclude atypical clefts due to their complexity (Calzolari et al., 2007).

Most atypical clefts are secondary or pseudo clefts occurring after the fusion of facial processes (Mazzola and Mazzola, 2014). Abnormal ossification of underlying facial bone resulting from altered mesenchymal differentiation results in developmental arrest and prevents normal growth of adjacent structures, leading to clefts. True atypical clefts include naso-ocular clefts, resulting from failure of fusion of nasal and maxillary processes, and commissural clefts (macrostomia) from failure of fusion of maxillary and mandibular processes. Developmental arrest of lateral extensions of forebrain with deficiencies in interplacodal area also result in true atypical craniofacial clefts but these foetuses often do not survive if the central nervous system anomalies are severe. Disruption of a normally developed facial structure can also occur independent of the planes of process fusion giving rise to atypical clefts as in amniotic band sequence (ABS). Considering the complexity, various topographic and pathomorphogenetic classifications exist (Broadbent et al., 1969; Tessier, 1976; van der Muelen et al., 1983; Allori et al., 2015). This study reports the phenotypic spectrum of atypical OFC from a single centre and attempts to relate the clinical diagnosis with other classifications. Risk factors, dysmorphism and associated anomalies are presented.

Materials and methods

In this cross sectional descriptive study over three years (August 2014 – July 2017) in a tertiary craniofacial unit from India, 500 consecutive children aged ≤18 years with OFC were enrolled. They were classified as typical or atypical and isolated or associated. Typical clefts namely cleft lip (749.1), cleft palate (749.0) and cleft lip with palate (749.2) were defined based on World Health Organisation (WHO) International Statistical Classification of Diseases (ICD-9&10). All others were grouped into atypical which included median, lateral and oblique clefts. Division into isolated or associated was based on absence or presence of other anomalies in any of the systems or requirement of extensive cosmetic correction. Bony clefts without soft tissue involvement, ear anomalies or tags without clefting and children with surgical corrections that precluded a syndrome diagnosis were excluded.

All children with atypical clefts underwent review of pedigree, birth and medical records and pre-operative photographs. Examination was focussed on the type of cleft, laterality, dysmorphology examination and evaluation for associated anomalies. Growth was assessed by WHO 2010 growth charts. Failure to thrive was defined as weight and weight-for-height less than third centile and micro- and macrocephaly as head circumference less than third centile or greater than 97th centile, respectively, for age and gender. Standard terminologies were used for description of dysmorphology (Allanson et al., 2009). Abdominal sonogram, echocardiogram and neuroimaging were done as indicated. Pattern of malformation and clinical diagnosis were established. Different classification systems were used to describe them topographically and morphogenetically (Broadbent et al., 1969; Tessier 1976; Mazzola and Mazzola, 2014). Statistical analyses was descriptive with frequencies (*n*) and percentages (%).

The study was conducted with approval of Institutional ethics Committee and informed consent for study participation and photographs were obtained from either of the parents and personal assent from children aged seven years and above.

Results

Of 500 children with OFC, 384 (76.8%) were isolated and 116 (23.2%) associated or syndromic. Twenty-one children had atypical clefts constituting 4.2% of all clefts and 18.1% of associated. All children with atypical clefts were associated. Oculo auriculo vertebral spectrum (OAVS) constituted the largest group with nine children. Others were Treacher Collins syndrome (TCS) phenotype in four, ABS in three, frontonasal dysplasia sequence (FNDS) in three, holoprosencephaly (HPE) sequence and heminasal aplasia without proboscis in one each. OAVS spectrum included hemifacial microsomia, oculoauriculovertebral dysplasia and Goldenhar syndromes. TCS phenotype included both complete and incomplete forms of Treacher Collins syndrome and acrofacial dysostosis.

Demography and risk factors

Majority were male (16, 76.2%). Eight of nine with OAVS and three of four with TCS phenotype were males. Median paternal and maternal ages were 32 and 27 years respectively. Advanced paternal age of ≥40 years was seen in two of TCS phenotype and young maternal age of ≤20 years in six which included two each of FNDS and ABS. Majority were first order (13, 61.9%) births; all of ABS were first born. In five, previous abortions were noted. Maternal factors included fever with rash in one, recurrent spontaneous abortion in one, first trimester acetaminophen exposure in two and gestational hypertension in two. No gestational diabetes was noted. No mother received preconception folic acid. There was no consanguinity in any of the families studied. Family history was positive in four children with OAVS and included preauricular tags (microform) and congenital heart disease in parent, congenital deaf mutism without ear anomaly and ABS in second degree relatives. Sibling death with multiple congenital anomalies was seen in the child with hemi nasal aplasia. Median birth weight was 2750g and ranged from 1200 to 3200g. Nine of 21 (42.8%) were born with low birth weight.

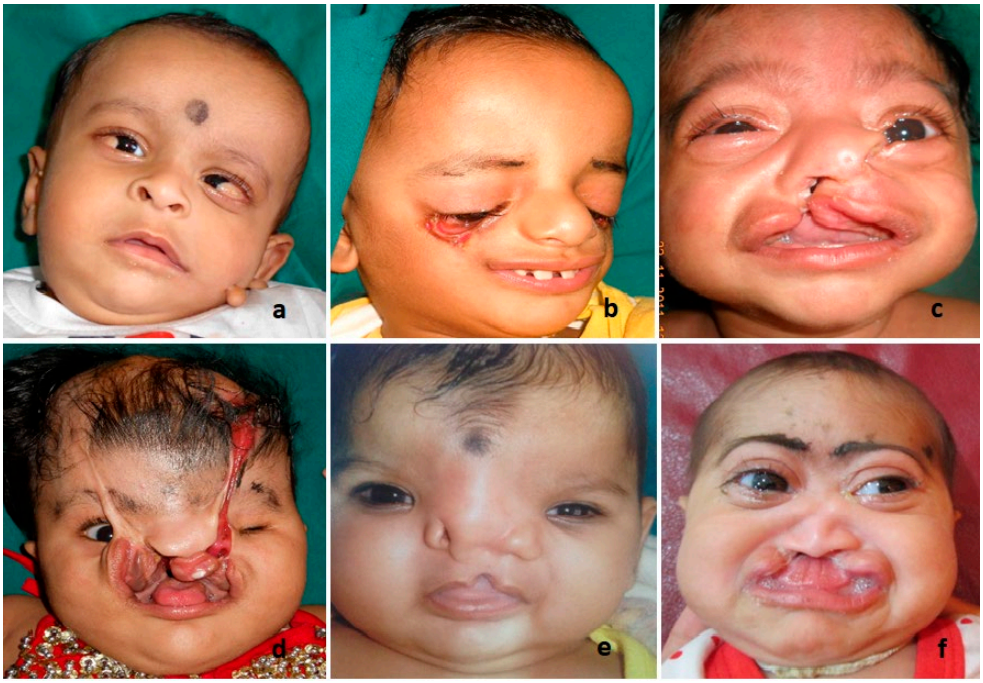

Figure 1. Atypical clefts in various topographic planes. a) Oculo auriculo vertebral spectrum with epibulbar dermoid and ear tags. b) Treacher Collins syndrome phenotype with downward slant, eye lid cleft, ectropion and maxillary hypoplasia. c) Amniotic band sequence with asymmetric facial, alae nasi and eyelid cleft. d) Amniotic band sequence with symmetric clefts with lateral displacement of canthi and upswept hair. e) Fronto nasal dysplasia sequence with hypertelorism and widows peak. f) Holoprosencephaly sequence with hypotelorism and absent philtrum.

medially drawn eyebrows, upswept hair (Figure 1d), widow's peak (Figure 1e) and projection of scalp hair onto cheeks. Nearly 12 of 21 (57.1%) children had failure to thrive. Other anomalies included upper airway obstruction in OAVS, congenital heart disease (ostium secondum atrial septal defect) in OAVS and HPE sequence, macrocephaly with developmental lag in ABS, microcephaly, seizures and severe developmental delay in ABS and HPE sequence. Acrania was also noted in one of ABS (Figure 3a). Neuroimaging showed semilobar type in HPE sequence and interrupted ventricular system and schizencephaly in two of ABS (Figure 3b-d).

Discussion

The atypical clefts seen here were either syndromic or part of sequence. Kalantar-Hormozi et al. (2017) reported atypical clefts in 80 (8.3%) of 964 with OFC over a ten year period with majority having Tessier 0 in the sagittal plane. The higher prevalence in their study compared to 4.2% in this report may be attributed to inclusion of 24 rare craniofacial clefts from one closed community. The ordered numbering system

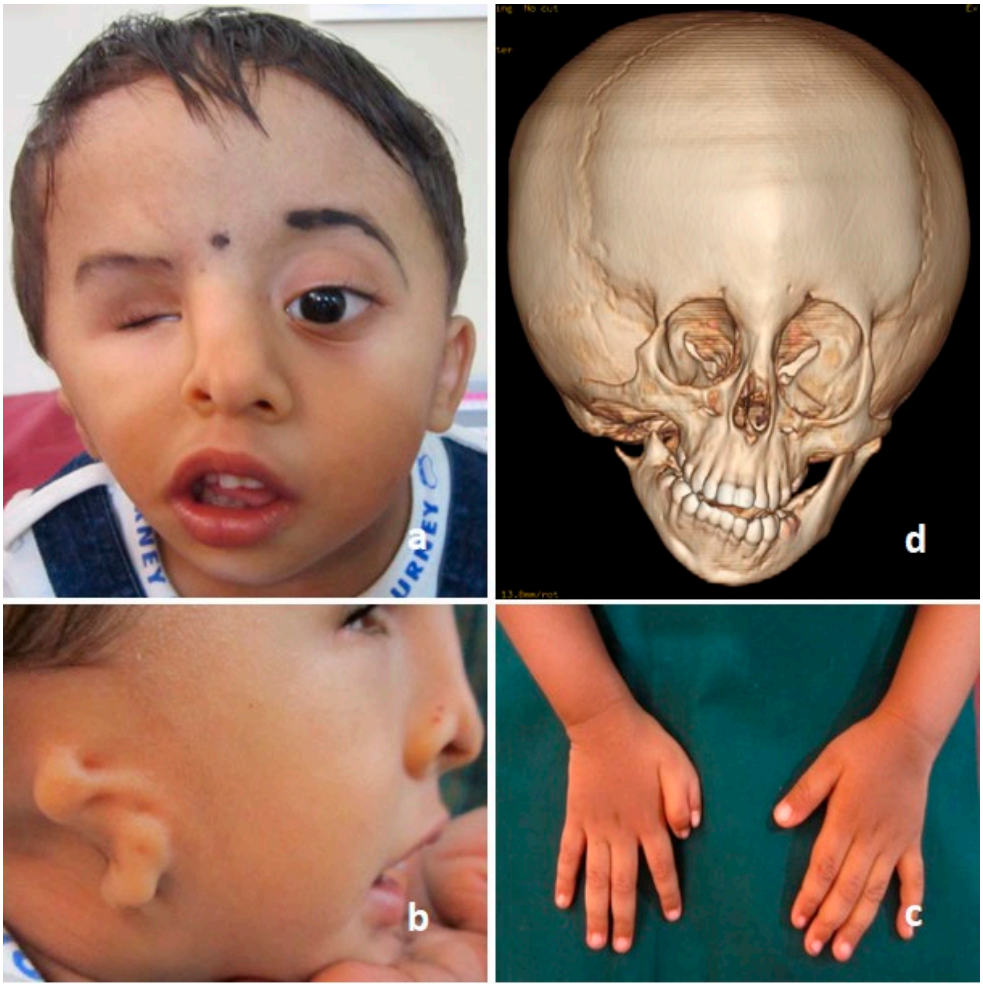

Figure 2. Child with oculo auriculo vertebral spectrum. a) Facial asymmetry, microphthalmia, heminasal hypoplasia, macrostomia. b) Microtia c) Pre axial polysyndactyly. d) Metopic prominence, orbit hypoplasia, hypoplasia of mandibular ramus and absent condyle in skull computed tomography three-dimensional reconstructed imaging.

of Tessier (1976) along definite axis with orbit as the reference point is the most widely accepted classification of atypical clefts. The morphogenetic classification is based on the chronology of developmental stages and recognition of pseudoclefts as craniofacial dysplasia (van der Muelen et al., 1983, 1990; Mazzola and Mazzola, 2014). The malformations were named by facial processes and bone involved. Differentiating a sporadic from an inherited condition by clinical synthesis is important for further workup and risk counselling.

Embryological development of face is complex with contributions from mesenchyme of the frontonasal process and the branchial arches. A disorder of craniofacial morpho-

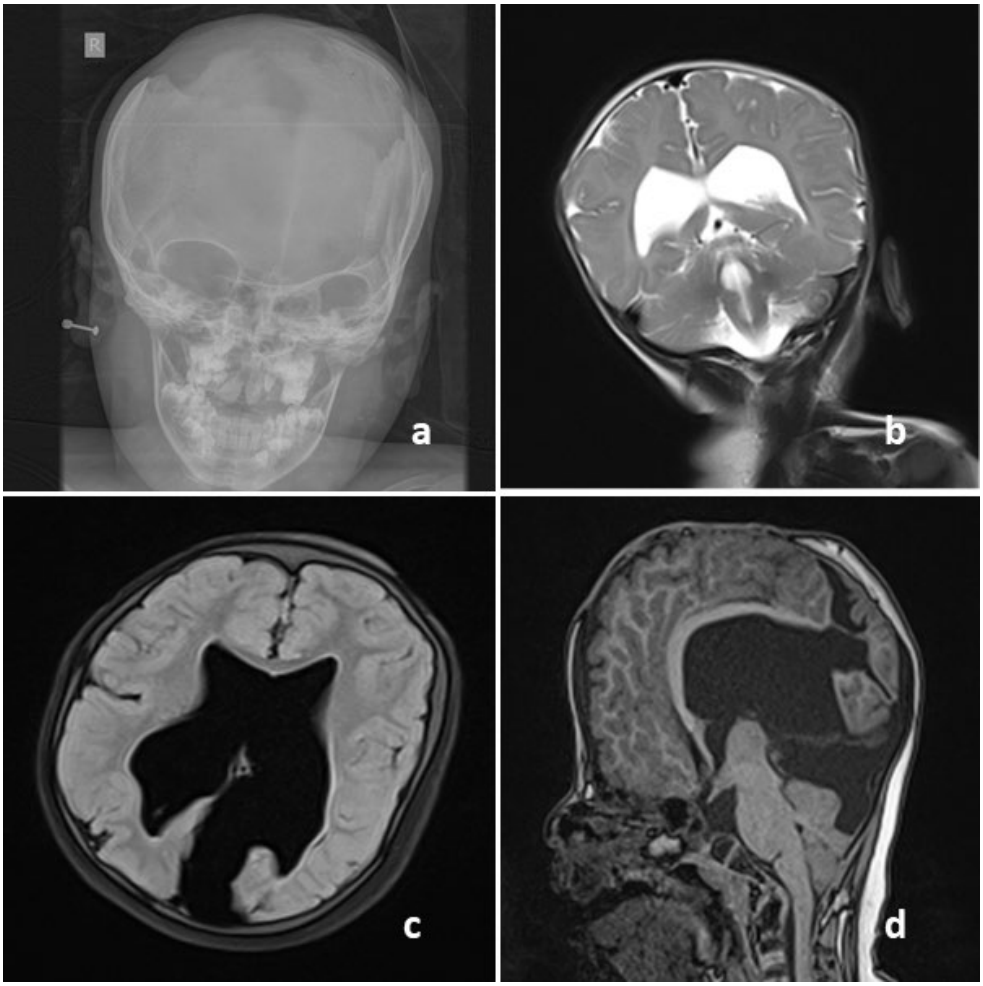

Figure 3. a) Acrania (skull radiograph). b) Semilobar holoprosencephaly (magnetic resonance T2 weighted coronal imaging) c,d) interrupted ventricular system with schizencephaly (magnetic resonance T1 weighted coronal and sagittal imaging).

genesis, OAVS is reported to have a prevalence of 1 in 3500 and is the second most common instance of OFC (Askar et al., 2001; Beleza-Meireles et al., 2014). It was the most common atypical cleft seen in the study. With wide phenotypic variations, there is no consensus on minimum diagnostic criteria, and microforms exist. Though considered sporadic, microtia and preauricular tags are reported in families; drug exposure and diabetes during pregnancy are reported risk factors. Bilateral facial involvement is reported between 10 and 33%, ear anomalies in 65% and epibulbar dermoids in 35%, and our results were comparable with these reports (Gorlin et al., 1990). Skin tags and epibulbar dermoids which are both choristomas correlate for laterality. Macrostomia, microtia or anotia, hypoplasia of maxilla and mandible are common to both OAVS and TCS pheno-

Table 1. Comparison of clinical diagnosis against various classifications in children with atypical clefts (*n*=21).

Clinical diagnosis	Broadbent et al., 1969	Tessier, 1976[a]	Mazzola, et al., 2014
OAVS *(9)*	Lateral	7	Malar hypoplasia
TCS phenotype *(4)*	Oblique	6, 7	Lateral maxillary with malar or mandibular hypoplasia
ABS *(3)*			
Case 1	Oblique	3, contralateral 1	Naso ocular
Case 2	Oblique	3,11	Naso ocular
Case 3	Median	1	Nasal
FNDS *(3)*	Median	0	Internasal
HPE sequence	Median	0	Internasal
Heminasal aplasia	Median	1	Nasal

OAVS – oculo auriculo vertebral spectrum, TCS – Treacher Collins syndrome, ABS – amniotic band sequence, FNDS – frontonasal dysplasia sequence, HPE – holoprosencephaly (n) – number of cases
aTessier 0-median, 1-paramedian, 3-oculonasal, 6-maxillary-zygomatic, 7-temporo-zygomatic, 11-medial orbital cranial

Table 2. Frequency distribution of dysmorphology in various clinical categories of children with atypical clefts (*n*=21).

Dysmorphism	OAVS	TCS	ABS	FNDS	HPE	HNA
Microphthalmos	1	-	1	-	-	-
Eyelid cleft	-	4	1	-	-	-
Epibulbar dermoid	5	-	-	-	-	-
Hypotelorism	-	-	-	-	1	-
Hypertelorism / telecanthus	1	-	2	3	1	1
Canthal dystopia	2	4	2	-	1	-
Bifid nasal dorsum and tip	-	-	-	3	-	-
Alae nasi cleft	-	-	2	-	-	-
Nasal aplasia / hypoplasia/ absent philtrum	1	-	1	1	1	-
Microtia / anotia	6	1	-	-	-	-
Ear tags	5	-	-	-	-	-
Pseudosyndactyly	-	-	2	-	-	-
Constriction rings, amputations	-	-	1	-	-	-
Polydactyly	1	-	-	-	-	-
Hemi vertebrae	1	-	-	-	-	-
Distinct hair or eyebrow pattern	-	1	3	1	1	-

OAVS – oculo auriculo vertebral spectrum, TCS – Treacher Collins syndrome, ABS – amniotic band sequence, FNDS – frontonasal dysplasia sequence, HPE – holoprosencephaly, HNA – heminasal aplasia

types. However bilateral involvement, down slanted palpebral fissures, cleft lower eye lid, lateral canthal dystopia and soft tissue groove corresponding to Tessier 6 characterise TCS phenotype. Advanced paternal age is known risk factor as in our study.

The reported prevalence of ABS is 1 in 11,200 births with a stable trend over 17 years (Orioli et al., 2003). ABS is presumed to occur by 12 weeks of gestation before the fusion of amnion with chorion and obliteration of extra-embryonic cavity. Craniofacial malformations are seen in one-third of all ABS and are the second most common structures involved after limbs. Very early in gestation, subsequent to the closure of anterior neuropore, disruption of migration of neural crest cells from the neural folds of anterior neural plate involves anterior calvarium, fronto-nasal and maxillary processes in addition to the developing brain (Higginbottom et al., 1979). The variability and severity of features are determined by timing and extent of amnion rupture. Symmetric clefting is however rare in ABS. Primi-parity and young maternal age are risk factors with an odds ratio [95% confidence interval] of 2.16 [1.25-3.72] and 1.5 [0.93-2.42] (Orioli et al., 2003). FNDS is documented in six multiple malformation syndromes and the features seen in our series are best described by frontorhiny which is recessively inherited (Jones et al., 2013). These disorders present as median cleft with hypertelorism. When median cleft lip occurs with HPE, it is a developmental defect of median craniofacium from anterior neural plate. Hypotelorism with wide palatal cleft, single nasal opening, absent columella and philtrum should suggest HPE median cleft sequence (Eppley et al., 2005). Heminasal aplasia results from agenesis of one of the nasal placodes around 28 days of gestation and is more often associated with proboscis.

To conclude, atypical clefting, though rare, constitute an important group of clefts in a craniofacial unit and have phenotypic heterogeneity. Knowledge of any of the topographic or morphogenetic classifications which are based on different principles would aid in the diagnosis.

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The authors have no competing interest to declare.

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