The embryological basis of craniofacial dysplasias

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Summary
Craniofacial dysplasia of a syndromic pattern can usually be classified into one of two easily identifiable groups. In the first group are those malformations of the craniofacial skeleton and soft tissues that are asymmetrical in form and in the other, those that are principally symmetrical. Clinical studies have demonstrated that affected subjects in the symmetrical group frequently improve in terms of facial appearance as growth and development proceed to maturity, while those with asymmetrical defects often deteriorate in this respect. Embryological studies on animal models of these malformations have shown that asymmetrical lateral facial dysplasia and symmetrical mandibulofacial dysplasia exhibit discrete and widely disparate causal mechanisms of malformation. Analysis of these mechanisms and their effects on subsequent growth and development has suggested significant variations in the timing and technique of reconstructive procedures which will enable the surgeon to produce the most effective results when used for the rehabilitation of the afflicted.

The congenital craniofacial dysplasias fall into two main groups: one with a strong familial history and usually with autosomal dominant transmission and a group in which the abnormality appears as an isolated event with no relevant family history. Many of these craniofacial dysplasias, familial or otherwise, have very similar clinical features and yet they appear to respond in very different ways to reconstructive surgery. This paper will describe some embryological investigations into the causal mechanisms which initiate these congenital craniofacial deformities and show how these studies have contributed to an understanding of the growth and development of these dysplasias, and the way in which they respond to surgical measures.

Lateral facial dysplasia
The first group is called lateral facial dysplasia and was known in the pre-Columbian era, c. 100 A.D., when the characteristic facies was recognized. This condition has no family history; it appears once in every 3500–4000 births and usually presents with a unilateral malformation which particularly affects the oto-mandibular structures. There is a deficiency of the malar bone and the zygomatic arch of the ear which may be reduced to just a small auricular tag, and a considerable skeletal deficiency, which is bilateral in about 30% of cases—it is invariably more severe on one side than on the other. It is never a symmetrical malformation (Fig. 1).

On examination, there is a defect in the body and ramus of the mandible behind the molar teeth, extending often in severe cases, right up to the coronoid process and the condyle, a defect of the malar bone, usually absence of the zygomatic arch, and often considerable deficiency in the area of the petrous temporal.

There is another closely comparable condition known as Goldenhar’s syndrome, where there are not only the skeletal and facial defects seen in lateral facial dysplasia, but often a co-existing coloboma, usually of the upper eyelid and sometimes anomalies of the cervical vertebrae. It is now believed that this Goldenhar syndrome is a variant of lateral facial dysplasia. Work by Ross (1975) at the Toronto Children’s Hospital has shown that by and large these patients do not always have the combination of coloboma and vertebral anomalies as expected, and it is very likely, in view of the similarities of Goldenhar syndrome and lateral facial dysplasia, that they are essentially the same disorder. There is no familial history in these cases, but as the patients grow older and reach puberty, so their condition on the affected side often deteriorates. Growth and development on the affected side lags behind growth on the unaffected or less affected side, and so the cosmetic defects become considerably worse.

The major defects in the craniofacial skeleton are found in the reductions in the temporal bone, in the ramus and body of the mandible, in the zygomatic arch and the malar bone; the auditory ossicles may either be absent, abnormal or fused together. There are also soft tissue defects. The masticatory muscles, the temporal and masseter are particularly involved; the parotid gland may be small or absent, and
occasionally there is not complete facial paralysis, but a weakness of the facial muscles on the affected side.

This dysplasia was called the 'first and second arch syndrome' for many years, but this was not a particularly good title, hence the name was changed to lateral facial dysplasia. Not all the structures involved are derived from the first and second branchial arches, e.g. the squamous temporal is unlikely to be so derived. Yet other structures which are derived from these arches, such as the hyoid bone which arises from the second, is never involved in this condition. In the U.S.A. the term 'facial microsomia' is used for this disorder.

Recently an animal model of this condition has been described (Poswillo, 1973) which, in terms of its external features, compares very closely with the human condition. In these experimental animals, approximately 30-40% showed bilateral defects, but these were never symmetrical. There were anomalies of the ear, gross reduction of the pinna, blind endings to the meatal tubes, defects of the malar bone and ramus of the mandible, demonstrated by comparison with the normal rodent. In the cleared and stained specimens, instead of the normal zygomatic arch and the condylar and coronoid processes of the mandible, there were gross defects in the ramus, in the malar bone, zygoma and temporal bone. Not only were there soft tissue defects comparable with man in these animal models which were produced by anti-folate drugs, but there were also skeletal defects very similar to those of lateral facial dysplasia. Having developed a model in which 100% of animals were deformed, it was then possible to study the sequence of events leading up to this malformation.

It was observed in the rodent at day 14, which corresponds roughly with day 32 or 33 in man, that the stapedial arterial system was beginning to develop. This replaces the first and second aortic arches after they shut down; from the stapedial arterial stem, which arises in the neck by the junction of the ascending pharyngeal and hyoid arteries, develop the supra-orbital, infra-orbital, maxillary, mandibular and hyoid branches. Later on, about day 42, these are annexed by the carotid system and the stapedial stem itself disappears. It was found that at the time of emergence of the stapedial stem in the rodent model, a haemorrhage appeared just at the developing stapedial anastomosis. This spread into the tissues, sometimes very small, sometimes very large, destroying large tracts of differentiated tissue destined to form the mandibular ramus, the middle and external ear, and all the structures in the vicinity of the oto-mandibular region (Fig. 2).

One could demonstrate a small, localized haematoma disrupting tissue destined to develop into the endaural cartilage, auditory ossicles and part of the external ear, also spreading to involve the condyle of the mandible. When there is a very large haematoma it displaces much larger tracts of tissue. Later, there is consequent phagocytosis of the extravasated blood and the defect is repaired by mesenchyme once again; but the delay is such that complete differentiation does not take place in that area, or if it does catch up at all, then primitive ears and
mandibular rami develop. Therefore many structures are incompletely formed, leading not only to skeletal defects but also to deficiency of the muscles. In a relatively minor example, comparing the affected with the normal side, the former shows a much smaller body of mandible, masseter and temporal muscle, showing that there has been damage both to muscle and the skeleton. This damage to the muscles plays an important part in the reduction of growth associated with this particular problem. Obviously, with a very large haematoma, local damage is more extensive, leading to very severe defects, particularly in the masticatory muscles.

With unequal damage on both sides, there is clearly a considerable difference in the residual effect, with marked asymmetrical deficiency of the body of the mandible and molar teeth and complete absence of the zygomatic arch and masseter muscle on the severely affected side. Hence, with absence of the muscular components of the functional matrix responsible for growth, it is understandable why, in these cases, as growth proceeds towards puberty, the greatly affected side lags behind and the condition becomes much worse as age progresses.

Owing to the absence of adequate musculature, most attempts at surgical reconstruction during the growth period are foredoomed to failure in this situation. This is why surgeons have had such poor success in attempting to restore to normal the facial appearance while growth is still active on the normal side and static on the severely affected side. When reconstructive surgery re-establishes facial symmetry during the growth period, this unilateral growth leads once again to progressive asymmetry and deformity.

Our understanding of the causal mechanism helps us to realize that in severe cases it is useless to try reconstructive surgery during the growth period. In lateral facial dysplasia, it is desirable to postpone any attempt to establish facial symmetry until growth on the affected or lesser involved side is almost complete.

**Mandibulofacial dysplasia (Treacher Collins syndrome)**

The second group of facial dysplasias include those of the Treacher Collins type, where there is strong familial tendency; it is interesting to compare the changes in the dysplastic facial skeleton and the differences in the causal mechanisms in the two groups. The Treacher Collins group was also recognized by the pre-Columbian Indians who understood the familial pattern; it is now known that about 50% of these cases have an autosomal dominant form of transmission.

In this disorder the skeletal changes are symmetrical in the craniofacial skeleton. There is some reduction in the ramus and condyle of the mandible, deficiencies of the zygomatic arch and malar bone (Fig. 3). But these are always symmetrical, as opposed to lateral facial dysplasia where they are invariably asymmetrical. The Hallermann–Streiff syndrome is another condition with a similar genetic background to the Treacher Collins type, with similar defects—hypoplasia of the malar bones, defects of the zygomatic arch, abnormalities of the
ear and some loss of the overall growth of the mandible. In Hallermann–Streiff syndrome there is symmetrical hypoplasia of the middle and lower thirds of the face.

To the embryologist this symmetry is most interesting for it indicates a different causal mechanism for the malformations, although the facial appearance is very similar to that of lateral facial dysplasia. One must seek for some other explanatory pathogenesis, operating very early in embryogenesis, unrelated to focal haematoma formation, and yet capable of producing symmetrical hypoplasia with defects in the skeleton. Johnston and Listgarten (1972) showed that a large proportion of the middle and lower thirds of the face arose in mesenchyme or ectomesenchyme which migrated into the branchial arches from the neural crest just after closure of the neural tube. They showed that many cells migrated under the ectoderm into the branchial arches where, in combination with the mesoderm, they contributed to the development of the skeleton of the middle and lower thirds of the face.

In attempting therefore to produce a suitable animal model of mandibulofacial dysostosis study was made of teratogenic agents which could influence the migration of the ectomesenchyme of the neural crest leading to greatly diminished branchial arches. These investigations were eventually successful (Poswillo, 1975) and revealed a further interesting feature on comparison of the normal animal with the Treacher Collins animal model. In the normal animal the otocyst lay adjacent to the second branchial arch. In the Treacher Collins model, the otocyst had drifted up, as a result of the spatial rearrangement of tissues which followed the death of the neural crest ectomesenchyme to the first branchial arch territory, locating the developing ear over the angle of the mandible instead of in its normal situation (Fig. 4). In the Treacher Collins syndrome we characteristically find the ears asymmetrically located low down, close to the angle of the mandible in first arch territory rather than in their normal second arch region. From the animal model of the Treacher Collins syndrome, it appears that the damage results from the early death of cells due to migrate into the branchial arches, so interfering with the development of the facial skeleton. A section of this region in the Treacher Collins model shows the otocyst high in the region of the first branchial arch with an area of dead tissue representing death of ectomesenchymal cells which should migrate into the branchial arches to produce the facial skeleton (Fig. 4).

The animal model shows the changed position of the ear which has been described, not only the spatial change to the region of the angle of the mandible, but abnormalities of the pinna which also appear in Treacher Collins syndrome, together with defects in the malar region and the mandible (Fig. 5). These are symmetrical deficiencies. In the mature animal skeleton of the Treacher Collins model, defects are seen in the zygomatic arch, the malar
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**Fig. 4(a).** Normal rat at term showing position of auricle and malar-mandibular contours. (b). Rat model of Treacher Collins syndrome showing malformed and malposed ear, malar flattening and altered craniofacial proportions.

**Fig 5(a).** Sagittal section of normal rat embryo at time of development of the branchial arches. Note dimensions of 1st and 2nd arches (1, 2) and neural crest cells in mesencephalon (arrow). (b). Sagittal section of rat model of Treacher Collins syndrome induced by vitamin A, showing cell death in vicinity of neural crest (arrow) and paucity of mesenchyme in branchial arches 1 and 2.
bone, the lateral wall of the orbit and dysplasia of the coronoid and condyle region of the mandible, by comparison with the normal morphology. The experimental model showed an attempt to produce a mandible that was functional; this was not completely successful as it did not have the normal angular, coronoid and condylar processes. It seemed that the result of the deficiency of neural crest ectomesenchyme was incomplete production of the normal, genetically-controlled facial skeleton.

This is, of course, exactly what is found in the Treacher Collins craniofacial dysplasia. The ears are abnormally placed, there are defects in the malar region with alterations in the slope of the eyelids, often colobomata of the lower lids (which again may be due to a deficiency in neural crest ectomesenchyme); there is an open bite and a face which, although recognizable as human, is not quite normal. Although we have these similar defects in the Treacher Collins syndrome and lateral facial dysplasia, they don't behave in the same way with respect to subsequent growth. In Treacher Collins syndrome, as the child grows towards puberty, the face likewise grows. At adolescence this progress may be measured and found to be symmetrical, but the growth pattern has not been quite normal; a cephalometric tracing of an afflicted child shows there are still differences of morphology with excessive downward and forward growth of the dysplastic bones of the facial skeleton when compared with a normal skull of about the same size (Fig. 6). The reason for this variation is that there is abnormal but symmetrical musculature attached to the mandible and posterior aspect of the maxilla in the Treacher Collins syndrome on both sides. Thus the motor units are symmetrical and although there is some reduction in the facial bones—hypoplastic bones beneath slightly abnormal muscles—together they do form a functional matrix which provides for symmetrical growth of the face. Hence, one may operate to reconstruct a child with Treacher Collins syndrome during the period of active growth, confident that growth will continue to be symmetrical. This important fact has made a considerable difference to the clinical management of these cases. In lateral facial dysplasia, as mentioned above, surgery during the growth period is usually contra-indicated. The animal studies of these two craniofacial dysplasias have therefore not only helped to distinguish them in terms of their causal mechanisms but have also contributed greatly to a more scientific approach to the timing and techniques of surgical reconstructive procedures.

A similar experimental approach to the study of animal models of Apert and Crouzon syndromes is currently in progress. Early investigations are encouraging and suggest that the models may lead to further information about their causal mechanism. Already, some of the exploratory surgical work based upon embryological studies seems to indicate that much earlier management of these disorders by cranietomy may lead to more positive facial development than the later sophisticated reconstructive operations introduced by Tessier (1967) during the last few years, procedures which have a much greater morbidity. Embryological studies designed to explore the mysteries of congenital dysplasias thus contribute not only to the body of knowledge concerning patterns of normal and abnormal development, but also to the rehabilitation of the handicapped child.

References


