The management and diagnosis of syndromic craniofacial cases

This article reviews syndromic craniofacial conditions and discusses the stepwise management of syndromic craniosynostosis from the antenatal period through to adulthood, including the management of premature skull suture fusion (raised intracranial pressure, abnormal head shape, shallow eye sockets) and midface hypoplasia (breathing, feeding, jaw and dental problems).

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Keywords

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Key points

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1. Craniosynostosis, premature skull suture fusion, results in an abnormally shaped head and can lead to restricted growth and development of the brain, developmental delay, breathing difficulties and eye problems.
2. The symptoms mostly result from midface hypoplasia and raised intracranial pressure.
3. Management revolves around maintenance of the airway, reduction of intracranial pressure, eye protection, feeding, and jaw and dental problems.

The role of sutures in the skull is to allow moulding and brain growth. As the brain grows and develops the skull bones are pushed apart at the sutures and bone is deposited. Once growth has completed, the sutures stabilise but do not fuse completely. In the condition of craniosynostosis there is premature suture fusion, restriction of growth at the level of the fusion and compensatory overgrowth in other parts of the skull. In the absence of other abnormalities or developmental delay, single suture synostosis (sagittal, lambdoid and metopic, **FIGURE 1**) is not considered syndromic in nature. However, if more than one suture is fused, an underlying genetic cause is likely.

Common, well-recognised syndromes include Apert, Crouzon, Pfeiffer, Saethre-Chotzen and Muenke syndromes. However there are many other more rare syndromes that feature craniosynostosis, such as Craniofrontonasal, Beare-Stevenson and Carpenter syndromes (**TABLE 1**). Frequently in syndromic cases of craniosynostosis, the most commonly synostosed suture is the coronal suture and this may be unilateral or bilateral, although other sutures may also be involved.

The overall prevalence of craniosynostosis is around 1:2,500 live births. Apert and Crouzon syndromes have a similar incidence: approximately 15 per million (a prevalence of 1:65,000), although reported incidences vary widely. Despite being autosomal dominant disorders, almost all cases of Apert syndrome and between 30-60% of cases of Crouzon syndrome occur *de novo*, where there is an association between new mutations and increasing paternal age.

The Alder Hey Children's Hospital catchment area has a population of approximately 10-15 million, 25% of whom are children. In 2013/14 the Alder Hey Craniofacial Team saw 37 new syndromic cases of craniosynostosis comprising:

- ten Apert syndrome
- six Crouzon syndrome
- fifteen Pfeiffer syndrome
- two Saethre-Chotzen syndrome
- two Muenke syndrome.

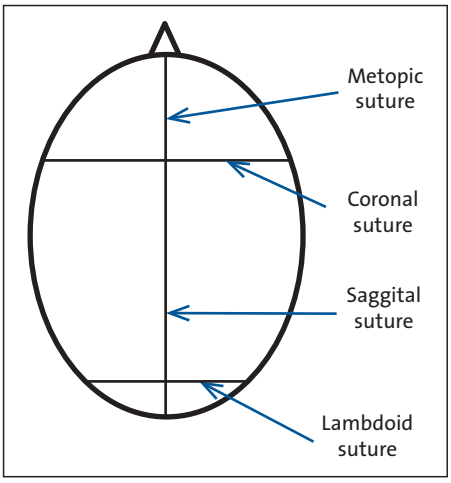

FIGURE 1 A diagram of the skull showing the cranial sutures.

In England and Wales patients with craniofacial syndromes are managed in four nationally commissioned centres at:

- Alder Hey Children's Hospital, Liverpool
- Great Ormond Street Hospital, London
- Oxford Children's Hospital
- Birmingham Children's Hospital.

Patients from Scotland and Ireland can also be seen in these centres. The national commissioning of care has resulted in much improved funding and the development of large teams providing comprehensive care for these complex patients. The teams generally comprise: neuro-, plastic, maxillofacial and

Syndromic craniosynostosis	Commonly associated features	Mode of inheritance	Mutated gene
Apert	Choanal stenosis, midface hypoplasia, mitten hands and feet, osseous syndactyly, proptosis, developmental delay in most cases	AD	*FGFR2*
Crouzon	Proptosis, midface hypoplasia, beak-shaped nose	AD	*FGFR2*
Pfeiffer	Crouzon-like face, broad thumbs or halluces, hallux varus	AD	*FGFR1* or *FGFR2*
Saethre-Chotzen	Facial asymmetry, ptosis, broad forehead, loss of frontonasal angle, beaked nose, prominent ear crus, broad thumbs or halluces, skin syndactyly, developmental delay in some	AD	*TWIST*
Muenke	Variable facies, hearing loss, developmental delay in some	AD	*FGFR3*
Craniofrontonasal	Hypertelorism, broad or bifid nose, wiry hair, nail ridges, narrow sloping shoulders	X-linked	*EFNB1*
Beare-Stevenson	Cutis-gyrata (hypertrophy and folding of the skin of the scalp), acanthosis nigricans, proptosis, choanal atresia, abnormal genitalia, anterior anus, umbilical and coccygeal anomalies	AD	*FGFR2*
Carpenter	Pre-axial polydactyly of feet, syndactyly, radial deviation of thumbs, hypoplastic middle phalanges, cardiac defects, hypogenitalism, umbilical hernias, obesity, ear anomalies	AR	*RAB23*

TABLE 1 The clinical features, inheritance and genetic changes associated with various craniosynostosis syndromes. Key: AD = autosomal dominant, AR = autosomal recessive.

otolaryngology (ENT) surgeons, an ophthalmologist, orthodontist, geneticist, speech and language therapist, psychologist and anaesthetist, respiratory paediatricians and clinical nurse specialists.

The antenatal period

Antenatal diagnosis is usually made via one of two ways:

1. Concerned parents with a family history
2. Identification of an abnormal head shape on antenatal scanning.

In families with a known genetic mutation, antenatal testing in the form of chorionic villus sampling or amniocentesis can be offered. The identification of an unusual head shape antenatally can be challenging as, despite suture synostosis, the head shape may remain relatively normal. This means that the majority of craniosynostosis cases remain undiagnosed until birth.

Syndromic cases are often identified at birth due to the complex nature of the condition and multiple anomalies that are apparent when the infant is born. Non-syndromic cases with single suture synostosis are often not identified until many months after birth when the progressive worsening of the head shape prompts referral, although there is often a history of altered head shape evident at birth.

The neurodevelopmental prognosis for infants with syndromic forms of craniosynostosis is variable and depends

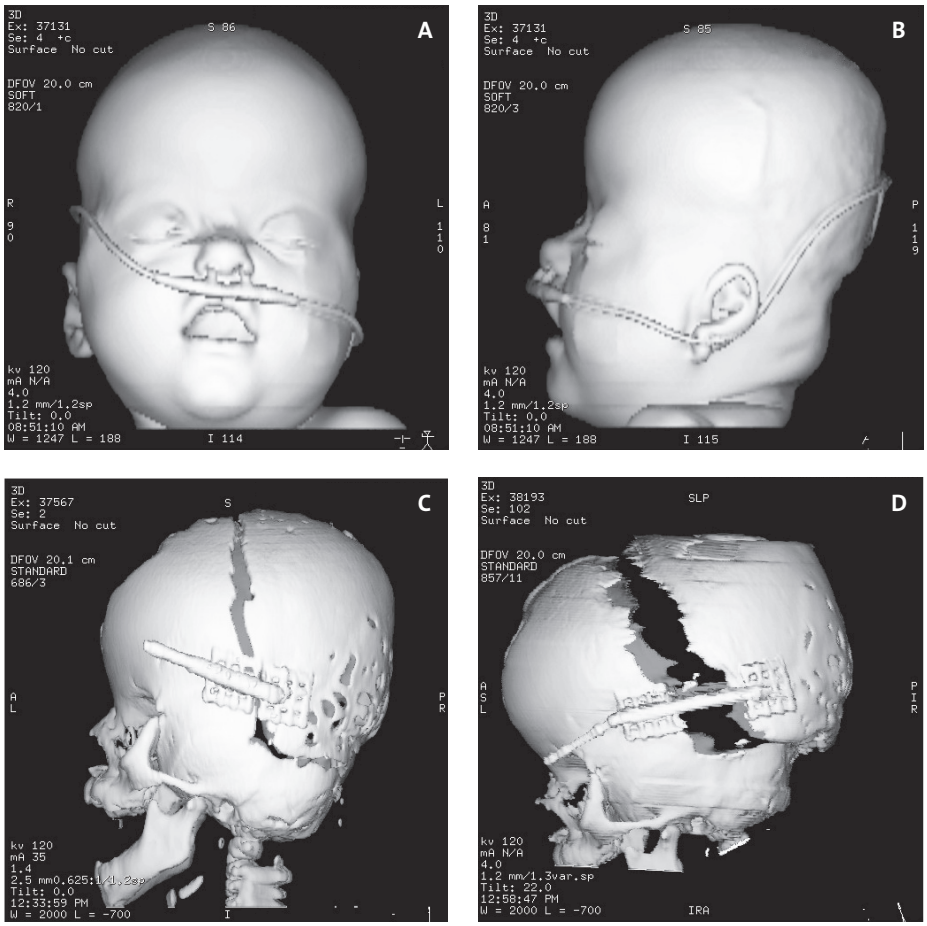

FIGURE 2 Posterior distraction in a patient with Apert Syndrome. A) and B) Reconstructions of a three-dimensional CT scan showing the typical appearance of a patient with Apert syndrome. C) The craniotomy with distractors in place. The arms of the distractor protrude through the skin which enables turning and distraction. One turn of the distractor arm translates to 0.5-1mm of distraction, depending on the make of the distractor. The degree of distraction is decided pre-operatively but is usually around 20-25mm. D) The completed distraction. The distractors are then left in place for three months for consolidation and removed during a second operation.

on the condition in question. Infants with some syndromes, such as Apert and severe forms of Pfeiffer syndrome, may have significant learning difficulties whereas most patients with Crouzon syndrome have normal learning and development. Prediction of outcome in some conditions may be extremely difficult. The complex nature of the difficulties faced by infants requiring multiple operations throughout childhood and the uncertainty around neurodevelopmental outcome in some cases, may lead parents to consider termination of pregnancy. However, the prognosis for infants with single suture, non-syndromic craniosynostosis is good and usually they will only face one operation to correct the abnormality.

Identification of fused sutures on antenatal scanning would, in fact, be more informative than looking for an altered head shape, however this does not form part of the routine 20 week anomaly ultrasound scan. If craniosynostosis is identified, careful examination of the face, hands and feet may aid diagnosis. Fetuses with Apert syndrome have syndactyly, brachycephaly (flattened back of the head), frontal bossing and midface hypoplasia, all of which can be identified by antenatal scanning. In this situation, an amniocentesis sample could be tested for mutations in the *FGFR3* gene, which is associated with Apert syndrome, and the parents could consider termination of pregnancy. All patients with scan findings suggestive of craniosynostosis should be offered antenatal counselling with a geneticist and a member of the craniofacial team.

Management in infancy

Most concerns in the newborn period centre on shallow orbits and a reduced airway due to midface hypoplasia. There may also be a problem with raised intracranial pressure if there is extensive suture synostosis or hydrocephalus. Management therefore revolves around maintenance of the airway, management of intracranial pressure, eye protection and feeding.

Management of intracranial pressure

Breathing issues have central and peripheral causes. Central causes involve neurological issues such as raised intracranial pressure secondary to multi-suture synostosis or hydrocephalus and Chiari malformation (herniation of the cerebellar tonsil through the foramen

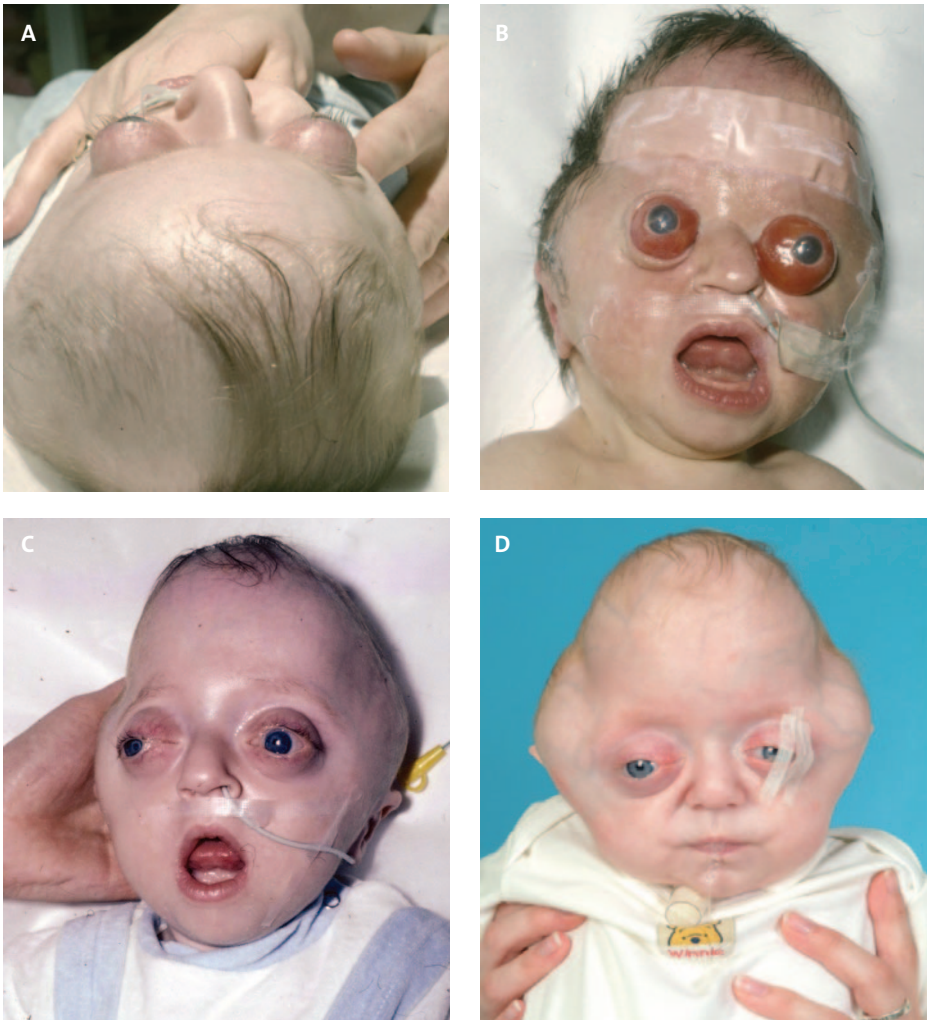

FIGURE 3 Examples of the management of some challenging ophthalmological conditions that occur in syndromic craniosynostosis. A) Bilateral shallow orbits giving rise to pseudo-proptosis. This is often more noticeable with coughing and Valsalva manoeuvres, when the globe/eye may sublux. The parents are often the first to notice this. If there is generally good lid closure, the parents can be taught to massage the lids to reposition the globe prior to considering lid surgery. B) Bilateral subluxation of the globes/eyes with extensive chemosis (swelling of the conjunctiva) and hazy corneas. Taping, gelpads and lubricants will not be sufficient and this is a sight threatening emergency that requires surgical closure of the eye lids. C) Medial and lateral partial lid closure (tarsorrhaphy) has been performed on the right eye only. The pseudo-proptosis and globe subluxation is often asymmetric. The lid surgery can be reversed with good cosmesis when the underlying shallow orbits have been corrected by craniofacial surgery. D) Medial and lateral tarsorrhaphies can be seen in the right eye. On the left, attempted lid closure by taping (there is risk of the tape touching the cornea and causing further damage).

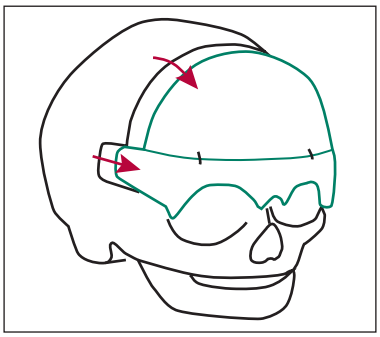

FIGURE 4 Schematic representation of correction of proptosis by frontal-orbital advancement (advancing the forehead and brow only).

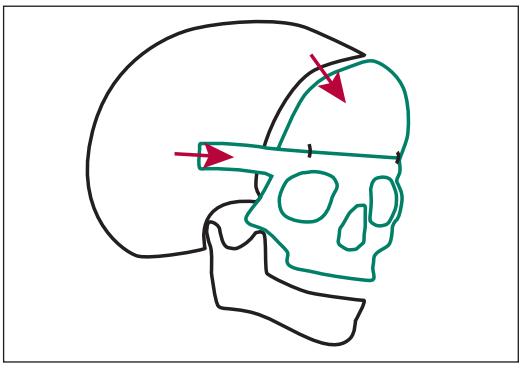

FIGURE 5 Correction of proptosis by monobloc advancement with on-operating table fixation (includes the midfacial bones).

magnum). Both result in pressure on the midbrain and reduced respiratory drive. Early management methods include insertion of a ventriculoperitoneal shunt or an endoscopic third ventriculostomy to treat the hydrocephalus and reduce intracranial pressure. Intracranial pressure can be reduced by increasing the size of the skull vault via enlargement of the posterior fossa (by remodelling or distraction) and foramen magnum decompression (in which a small part of the skull is removed to enlarge the foramen magnum and the posterior arch of the first cervical vertebra is removed).

Posterior vault remodelling involves the release of the posterior skull bones (posterior parietal and occipital) and on-operating table fixation (securing the skull bones in their final position using mini plates and screws). Distraction is performed by insertion of either an external distractor or internal springs, which provide graduated distraction. The distractor can be turned externally increasing the width of the craniotomy (**FIGURE 2**). Once the desired increase in volume is achieved, the distraction ceases and a period of consolidation begins.

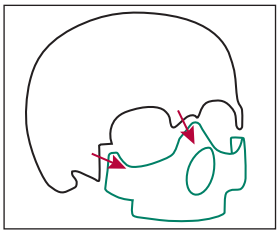

FIGURE 6 Midface advancement by Le Fort III osteotomy.

Peripheral causes of respiratory problems

Peripheral anatomical causes of respiratory problems include choanal atresia (blockage of the nasal passages by soft tissue or bone), midface hypoplasia and tracheomalacia (softening of the tracheal cartilages). Patients may require choanal dilatation or a tracheostomy.

Management of the eye

Management of the eye involves ensuring that there is adequate lid closure in order to protect the cornea. This may involve lubrication, taping and the use of an eye shield. Tarsorrhaphy (suturing of either part or all of the eye lids, shortening or closing the palpebral fissure to improve protection of the cornea) may be required at a later date (**FIGURE 3**).

Correction of proptosis involves alteration of the depth of the orbit by advancing either the forehead (frontal-orbital advancement) or the midface (monobloc advancement). At Alder Hey, frontal-orbital advancement (**FIGURE 4**) is performed at approximately 14-18 months of age and monobloc advancement later on in life (**FIGURE 5**), most commonly after 10 years of age in order to reduce the chance of bone recession post-operatively. Occasionally, the monobloc advancement is carried out at an earlier age if the

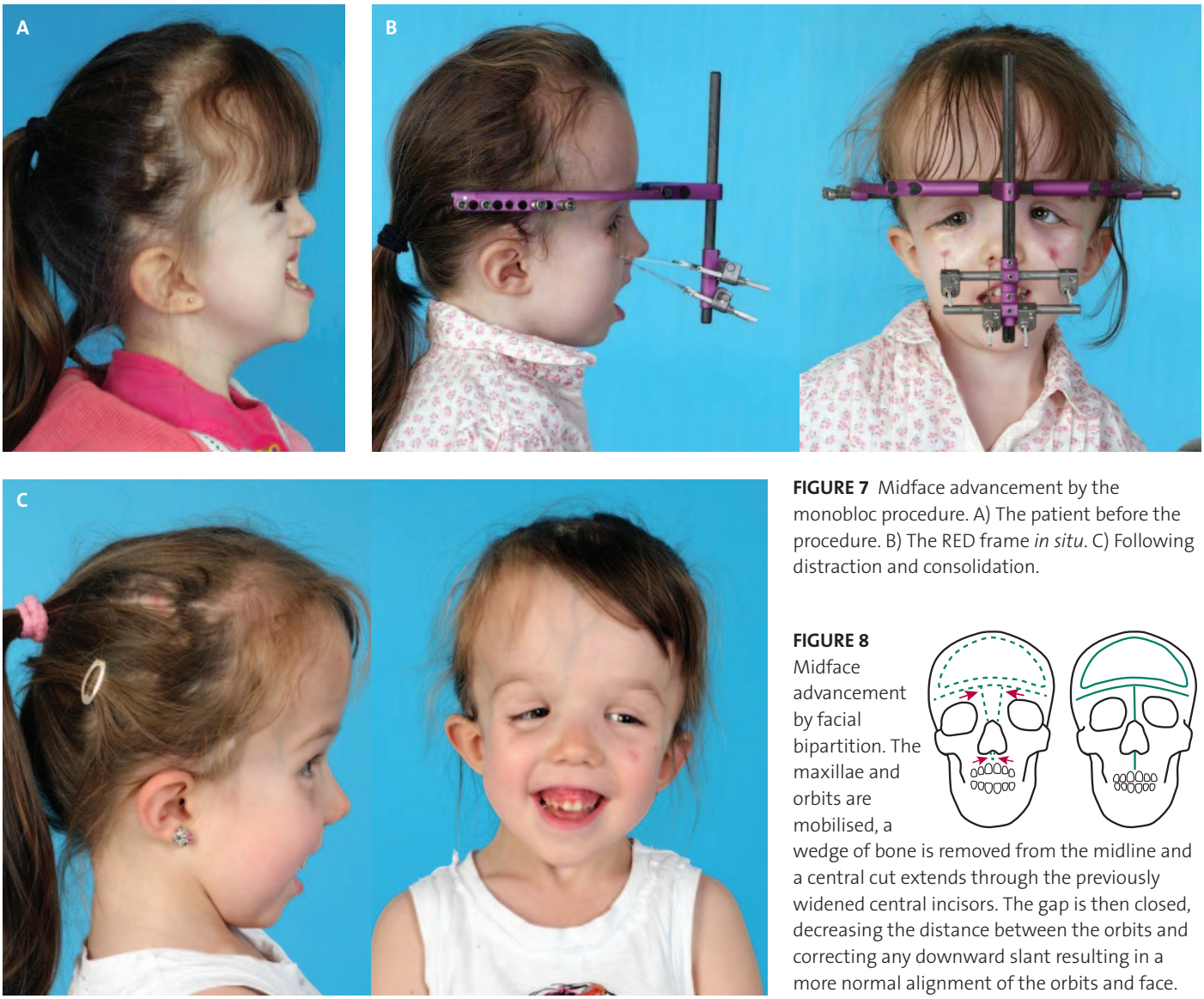

FIGURE 7 Midface advancement by the monobloc procedure. A) The patient before the procedure. B) The RED frame *in situ*. C) Following distraction and consolidation.

FIGURE 8 Midface advancement by facial bipartition. The maxillae and orbits are mobilised, a wedge of bone is removed from the midline and a central cut extends through the previously widened central incisors. The gap is then closed, decreasing the distance between the orbits and correcting any downward slant resulting in a more normal alignment of the orbits and face.

patient's breathing problems indicate an earlier procedure is required.

Feeding

The majority of these patients are fed by nasogastric tube until airway protection is obtained and safe swallowing is established. Alternatively a gastrostomy tube can be inserted.

Further interventions that may be required in infancy include cleft palate repair and hand surgery, for example in Apert Syndrome. At Alder Hey, all patients are seen by the specialist speech and language therapist who has expertise in these complex cases and often reviews the cleft lip and palate patients as well.

Management in childhood

Throughout childhood, there is continued management of the airway, eyes and intracranial pressure. Speech, dental development and psychological issues may also warrant attention.

At this point, the airway may be managed by midface advancement by Le Fort III osteotomy, monobloc frontofacial osteotomy or facial bipartition, depending on the circumstances of each patient and decided upon in a multidisciplinary setting.

Le Fort III osteotomy

This procedure involves the separation of the maxilla from the skull base and advancement of the midface (**FIGURE 6**). The advancement may be performed on the operating table or by distraction.

Monobloc frontofacial osteotomy

The monobloc procedure involves releasing the forehead and midface skeleton and then gradually moving it forward (**FIGURE 7**). Distraction and stabilisation of the monobloc advancement is achieved by using a rigid external distraction frame known as the RED frame (KLS Martin, Germany). Distraction occurs over a period of approximately 25 days at a rate of 1mm per day followed by a consolidation period of three months.

Facial bipartition

Facial bipartition is used to correct hypertelorism (abnormally large distance between the orbits) and upper jaw alignment (**FIGURE 8**). This procedure is often combined with the monobloc advancement.

Management in adolescence

In adolescence there may be reduced maxillary growth but continued mandibular growth which results in a class III jaw relationship and class III malocclusion, where the lower jaw is relatively prominent with respect to the upper jaw and consequently the teeth do not meet properly.

Management in adults

In adulthood slight recession of the previous frontal-orbital advancement may mean that forehead augmentation is required. This involves insertion of an implant over the forehead to enhance the forehead's contour. Rhinoplasty is also offered at this stage along with other aesthetic procedures.

Patient consent

The author received permission to publish these photographs from the patients' representatives.

Bibliography

Hayward R., Jones B., Dunaway D., Evans R. (eds). *The Clinical Management of Craniosynostosis.* London: Mac Keith Press; 2004.