Case Discussion: Cleft Lip and Palate

Epidemiology

Cleft lip (CL) and palate (CP) occurs as part of many other malformation syndromes in a non-specific manner more frequently than would be expected. The aetiology of isolated clefts, without syndromic features or family history, however, is likely a result of genetic and environmental factors.
The population incidence is

- 1 in 500 - 1 in 1000 for cleft lip (with or without cleft palate). It is unilateral in 80% of cases with the left side more commonly affected. Males are often more severe.
- 1 in 2500 for isolated cleft palate. The spectrum of abnormalities ranges from bifid uvula to submucous cleft to velopharyngeal insufficiency (regurgitation of milk in children to nasal speech in adults).

Genetics

- Inheritance is most often polygenic / multifactorial.
- Syndromic associations need to be specifically considered and excluded.
- Numerous studies have shown that cleft palate alone runs in most families separately from cleft lip with or without cleft palate.
- Van der Woude syndrome (VWS) is the most common syndromic form of CL/P. Inheritance is autosomal dominant due to mutations in the IRF6 gene. It is characterised by lip-pits with or without oligodontia. Penetrance is highly variable.
- A number of X-linked families with cleft palate and ankyloglossia (tongue-tie) have been described and more recently the gene identified.
- Median cleft lip should be considered as a separate genetic entity with its own syndromic associations.
- The risk for sibs of a patient with CL/P is less when there is no family history (2.2%) than the overall risk to sibs (4%).

Case Scenario

A thirty-six year old male attends the genetic clinic regarding his history of cleft lip and palate. He wishes to know whether a genetic test is possible to determine his risks of having a child with CL/P and if prenatal testing is possible. He feels very strongly that the stigma of having had several operations to repair the defect and the resulting facial scars led to a lot of stigma and teasing as a child. He would not want to bring a child into the world that had a similar problem. If he knew a child was affected he would want to terminate the pregnancy.
Although not sure, he believes his grandfather, who died in the World War, also have had a cleft lip.

Clinical and Genetic Counselling Issues

- Confirmation of the diagnoses in affected relatives may be possible by examining family photographs.
- Careful examination is required to exclude Van de Woude syndrome or other clefting syndromes. (See Table).
- The consultand is requesting prenatal testing, which is only possible if a specific gene mutation can be identified in him.
- Prenatal diagnosis by USS would not be reliably possible until 20 weeks at which time a late termination would be needed.
- Counselling for prenatal genetic testing and screening USS should include his partner, with discussion of the advances in surgical techniques, psychosocial issues and the timing of surgery.

Investigations

- Mutations in MSX1 have been found in 2% of non-syndromic CL/P cases with a dominant history.
- Routine chromosomes if CL/P and another abnormality.
- FISH studies for 22q.11 deletions
- Consider telomere analysis if there is congenital heart disease.
- DNA for IRF6 gene in VWS if lip-pits suspected.
- Cardiac echo if any heart murmur (22q11 deletion syndrome)
- Eye examination if myopic (Stickler's syndrome)
- Further investigations are largely guided by the clinical findings and the reader is directed to a more specialist test book

Ethical Issues

- The gentleman's partner needs to be included in the counselling
- The absence of a specific mutation may preclude any prenatal testing
- A late termination after 20 weeks for a treatable condition of normal intelligence with good cosmetic results may be unacceptable to medical and nursing staff and some obstetricians may refuse termination.
- Improvements in surgical techniques have been significant over the last 36 years. The gentleman's experience in childhood is unlikely to be repeated.

Screening

- The use of high resolution ultrasonogrpahy (USS) has replaced fetoscopy for early diagnosis.
- USS at 20 weeks gestation should be considered the screening tool for pregnancies at high risk of a serious clefting disorder reoccurrence.
- Small clefts may still be missed even in specialist centres.
- Cleft palate is difficult to detect by USS in pregnancy.

Therapeutic Intervention

Recent case control studies have shown that periconceptual folate supplementation has a 47% risk reduction in CL/P in offspring of when compared to no maternal folate supplementation.

- A dose of 5mg/day is recommended for women with a previous occurrence and 400mcg/day where there is no prior history.

References

Van Rooji, JA., et al Periconceptual folate intake by supplementaion and food intake reduces the risk of non-syndromic cleft lip with or without cleft palate. Prev med 2004. 39, 689-694.

Reoccurrence Risks for isolated CL and CL/P

Relationship to index case	Reoccurrence risk (%)
Sibling unilateral CL	2-3
Sibling unilateral CL/P	4
Sibling bilateral CL/P	5-6
Two affected siblings	10
Affected sibling and parent	10
Affected parent	4

Table 2

Syndromic diagnoses to consider

- Piere-Robin sequence
- Van der Woude Syndrome
- Stickler syndrome
- 22q.11 deletion syndrome
- Treacher-Collins syndrome
- X-linked cleft palate and ankyloglossia
- Opitz syndrome
- Ectrodactyly, ectodermal dysplasia and clefting syndrome
- Kabuki syndrome

Prenatal scan pi cod cleft lip
pic of cleft lip
Pic of cleft palate/bifid uvula
Lip pits