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Special Review Article

Cleft lip and palate: Care configuration, national registration, and research strategies

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ABSTRACT

A child born with a cleft lip and palate will face 20 years or more of hospital care and surgery. This is a global problem with approximately 10 million people affected worldwide. Various models of care exist around the condition, and the best configurations of services within an economy need to be optimized. We provide examples of how centralized care can improve outcomes and provide an opportunity to establish national registries, and then emphasize the opportunities for building research platforms of relevance. The default of any cleft service should be to centralize care and enable cleft teams with a sufficient volume of patients to develop proficiency and measure the quality of outcomes. The latter needs to be benchmarked against the better centers in Europe. Two areas of concern for those with cleft are morbidity/mortality and educational attainment. These two issues are placed in context within the literature and wider approaches using population genetics. Orthodontists have always played a key role in developing these initiatives and are core members of cleft teams with major responsibilities for these children and their families.

1. Introduction

The impact of Coronavirus Disease 2019 will have left many orthodontists reeling from some devastating financial issues and limited provision of care for their patients. It will be important as we emerge from this virus pandemic that the most vulnerable groups of our patients are given priority. This will include children born with cleft lip and/or palate (CL+/P) and those with significant craniofacial issues. Orthodontists have played a significant role in changing the care of these children in several health systems across the world. They are often recognized as custodians of data, have been willing to ask questions, and make brave challenges on the quality of outcomes. There are significant benefits from improving treatment for these children, particularly in centralized models, and that can yield improved outcomes as well as establishing a platform for registration and research. This paper seeks to demonstrate contributions from orthodontists and highlights information of relevance to parents and families of those living with cleft.

2. Epidemiology and etiology

CL+/P is a global issue in which approximately every 3 minutes, a child will be born with some form of orofacial clefting. In the

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world, more than 10 million lives are affected by the condition. The cause of clefting is unknown; there are known racial and geographic variations and there are associations with environmental exposures and socioeconomic status (for seminal reviews see Mossey et al. [1]; Dixon et al. [2]). New Zealand Maori, American Native, and Asian populations have the highest reported birth prevalence rates, which are often as high as 1 in 500 [2,3]. European-derived populations have intermediate prevalence rates at approximately 1 in 1000, and African-derived populations have the lowest prevalence rates at approximately 1 in 2500 [1].

The frequency of CL+/P also differs by gender and laterality. There is a 2:1 male-to-female ratio for clefts involving the lip, approximately a 1:2 male-to-female ratio for clefts of the palate only, and a 2:1 ratio of left- to right-sided clefts among unilateral cleft lip cases. Approximately 70% of all cases of CL+/P and 50% of cases of cleft palate only are nonsyndromic. Orofacial clefts can be divided by phenotype into cleft lip (CL), with and without cleft palate, and these clefts may be complete or incomplete, unilateral (UCLP), or bilateral (BCLP). Cleft palate (CPO) can also occur in isolation [2] (Fig. 1).

The frequency of these phenotypes varies by population, and it highlights the importance of registrations and surveillance because these specific entities may provide epidemiological and genetic clues as to cause and best treatment. In European populations, approximately 50% of all clefts are CPO, 10% CL, 25% UCLP, and 10% BCLP. The remaining 5% are median clefts or variants. CL and CPO may have different etiologies, and there is evidence from familial studies and epidemiology that there are genetic differences. Twin studies have shown that concordance for CL, cleft lip and palate (CLP), and CPO are higher in monozygotic than dizygotic twin pairs, suggesting a genetic influence. Recurrence risk in families is a further pointer to genetic influence in nonsyndromic clefting [4]. Accurate phenotyping is crucial to understanding both the epidemiology and etiology of CLP because the power to detect effects is weakened when all clefts are treated as a single entity.

Genome Wide Association Studies (GWAS) search the genome for single-nucleotide polymorphisms that occur more frequently in people with a particular disease/trait than in people without the disease/trait. They are a promising way to study complex, common diseases in which many genetic variations contribute to a person's risk. GWAS have provided major advances, but the early published reports treated CL+/P as one group and had relatively low numbers [5–7]. This reflects how difficult it is to collect large samples for those born with cleft. There is also the issue of whether the cleft types are genetically distinct and how are subclinical phenotypes accounted for? Microforms of cleft can be seen in teeth, lip muscle defects, and lip pits, as well as three-dimensional facial images and brain imaging. There are emerging strong and coherent arguments for considering detailed dental phenotypes as an important part of describing clefts and thereby enhancing genetic studies. There are also surrogate measures, such as speech, hearing, educational attainment, social adjustment, and professional development [2]. If detailed information is to be collected longitudinally, then cohort studies are needed with significant funding and commitment. We have achieved this through service development and reconfiguration, and this has helped answer the question as to whether all clefts are the same?

There is good evidence that different subtypes of orofacial cleft have distinct etiologies, but the precise molecular mechanisms underlying these are unknown. Given the key role of epigenetic processes, such as DNA methylation, in embryonic development, it is likely that aberrant DNA methylation may also play a part in the development of orofacial clefts (*easy start to understanding epigenetics*) [8]. We used blood samples from children with different cleft subtypes to demonstrate distinct DNA methylation profiles and found four genomic regions differentially methylated in CL compared with CLP, in CPO compared with CLP, and in CPO compared with CL. These regions included several that mapped to genes that have previously been implicated in the development of orofacial clefts (for example, *TBX1, COL11A2, HOXA2, PDGFRA*). These distinct methylation profiles in different cleft subtypes might reflect differences in their etiologies, or causal genetic and environmental factors [9,10].

3. Infrastructure and capacity to treat CLP

Treatment of a child born with a cleft requires significant input from several specialists over 20 years and beyond. The most pressing initial needs deal with feeding and support for the family, which usually comes from specialist nursing; thereafter, surgical repair is required, as well as early preventive advice from pediatric dentists. Surgical repair of the lip is usually at 3 months, the palate at 6 to 9 months, with alveolar bone grafting required as the upper canine starts to develop, usually at approximately 7 to 9 years of age. Further surgery also may be required to aid speech, revise primary surgery, and/or repair fistulae. Speech and language

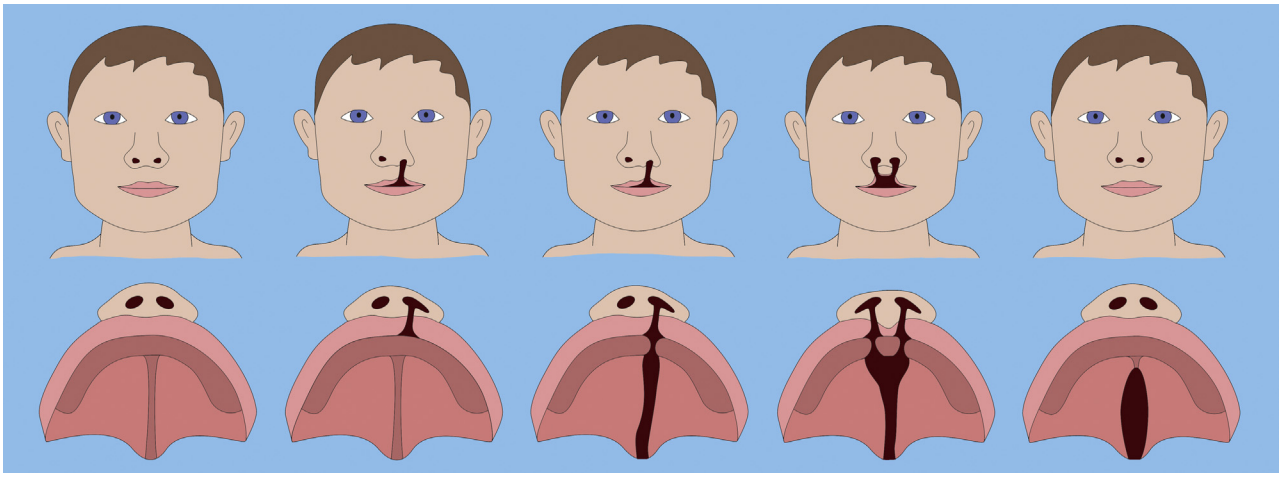

Fig. 1. Cleft phenotypes showing an intact and normal palate: CL, unilateral cleft lip and palate (UCLP), bilateral cleft lip and palate (BCLP), and CPO. (Illustration by Dr. Hywel Naish.)

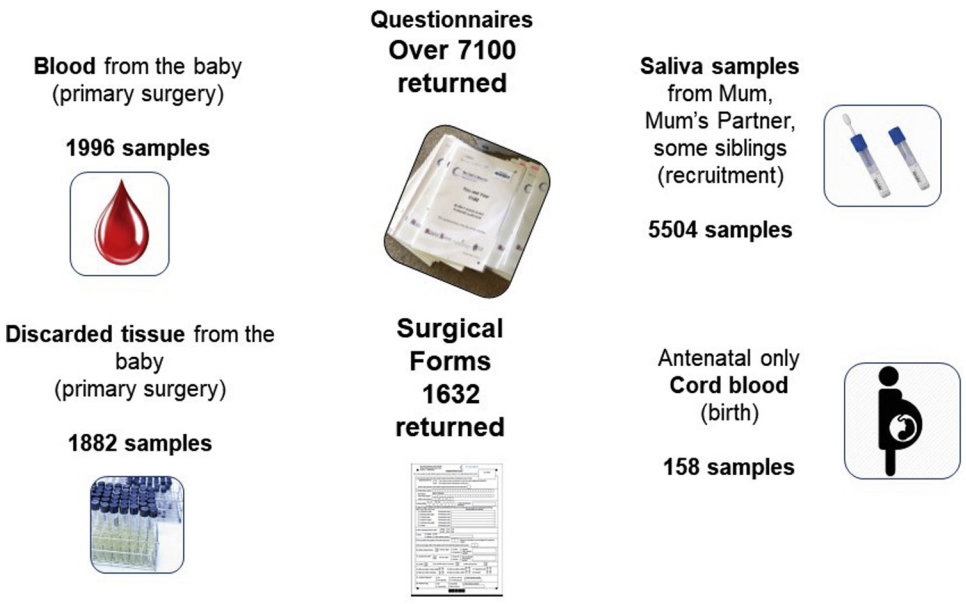

Fig. 2. The Cleft Collective is a longitudinal cohort study of children born with cleft and their families in the United Kingdom. Blood is collected from those diagnosed through antenatal scans (cord blood) and from the child at operation, as well as discarded tissue. The cleft teams return surgical details. Families are asked to provide saliva and fill in questionnaires. The figures to date are shown against samples and questionnaires. The study is ongoing.

therapy, psychology, restorative dentistry, and orthodontic treatment are needed variously as the child develops. These different specialties work best as a team, with appropriate integration of professional services support staff [11].

Three decades ago in the United Kingdom it was recognized that outcomes were not as good as those seen in the best European cleft centers [12], and various professional and parent help groups succeeded in pressuring the government to commission a study known as the Clinical Standards Advisory Group (CSAG). After a clear demonstration of poor outcomes, the government recognized there was a need for change [13].

Essentially the 57 cleft centers were reduced to 16 managed clinical networks across the United Kingdom and the 1200 children born each year with some form of cleft are treated in these centers. This has allowed proficiency and efficiency to develop, and a follow-up study some 15 years after this centralization of services showed up to a 50% improvement in some outcomes. There is no room for complacency, there are still some areas of care that need attention. For instance, dental caries remained at very high levels post-centralization, and a significant preventive strategy needs to be developed for this wholly preventable disease [14]. Nonsyndromic children born with CL+/P tend to have a lower oral health–related quality of life than a general noncleft population, which extends into adulthood [15].

4. Centralization of care and research

There have been other positive consequences of this centralization in relation to research. One of the recommendations from the CSAG report was to develop a national registry for children born with a cleft. This registry (Cleft Registry and Audit NEtwork, CRANE, www.crane-database.org.uk) has been running since 2000 and now has more than 22,000 cleft birth registrations. If this is compared with the excellent Scandinavian registries in Sweden and Denmark, then the scale is significant. It took more than 50 years for the Danish registry to recruit 7000 children, and by dint of a slightly larger population, Sweden recruited nearly 8000 cleft births over 50 years. These two registries are made even more powerful through the ability to link to other health databases, as well as social data such as education. The United Kingdom by virtue of its population size is ideally placed to recruit large numbers of cleft births and should be able to answer questions on the treatment of these children as well as the outcomes.

The second major UK initiative was the development of a cohort study for children born with CLP that now recruits families to provide the information on lifestyle environment and treatment. Observational cohort studies also can be used as a high-quality design for answering questions around prevalence, natural history, and risk factors. This cohort study (known as the Cleft Collective, http://www.bristol.ac.uk/cleft-collective/) started in 2012 and was funded through a medical charity, The Scar Free Foundation. In collaboration with those born with cleft and their families, as well as the clinical teams, research protocols and questionnaires were developed and implemented within all UK cleft teams once ethical approval had been obtained. Recruitment to the study and data collection are ongoing, with more than 9000 participants from more than 3000 families recruited to date. The progress of the collection is easily understood from Figure 2. In addition, there is a nested speech and language study within the Cleft Collective (Cleft Collective Speech and Language [CC-SL] study). The data collected form a comprehensive resource of information about individuals with CL+/P and their families and is constantly expanding. The resource comprises biological samples, speech audio recordings, medical and educational records, and parent- and child-completed questionnaires. It is available for clinical and academic communities to access and use to address a range of cleft-related research questions. More information on the study and how to access the dataset is available at www.bristol.ac.uk/cleft-collective/professionals/access/. This initiative provides the basis of a longitudinal cohort study, many future projects, and worldwide collaborations [16,17].

These approaches, where services are reconfigured to provide improved outcomes and coupled with a research agenda that includes national registration and a cohort study are unique, but none of this would have been possible without previous seminal work by Professors Gunvor Semb and Bill Shaw. The Eurocleft studies showed the importance of intercenter comparisons and started to relate volume and outcomes [12]. This certainly informed the need

for CSAG in the United Kingdom, and the subsequent "Americleft" [18] and New Zealand studies [19,20] followed similar lines. In New Zealand, where there are 100 cleft births a year, patients are treated in five centers; some outcomes are very poor and a centralized model is the most obvious way forward. The difficulties in creating centralized care involve geography, travel, and access as well as a political will. Private health care systems add another layer of complexity because financial imperatives often stymy clear evidence. Other initiatives from Bill Shaw and Gunvor Semb have included herculean tasks such as Scandcleft [21] and the timing of palatal surgery [22], where operative techniques and timing of surgery are scrutinized. These studies require global collaborations and significant finance but are starting to indicate that operator skill is of paramount importance and can override technique and timing. Two areas are highlighted to demonstrate why we need national registries and large cohort studies to answer sensitive questions accurately and confidently.

5. What information can we give patients and families?

When a child is born or diagnosed antenatally with a cleft, parents are shocked and distressed but after the initial impact they generally will want to know what the best treatments are (and where these are delivered), what has been the cause, and what does the future hold for their child? None of these are easy to answer, but the information that parents and those born with cleft are given needs to be based on best available evidence. The relatively low incidence of clefting results in many studies recruiting low numbers of cases in which results and interpretations may then be spurious.

Parents would be concerned if they were told "affected children have higher morbidity and mortality throughout life than do unaffected individuals," which is derived from a single short-term study (2 years) of 347 cases of CL+/P [23]. After consideration of terminations and late fetal loss, there was a 1% overall perinatal mortality rate for all children in the region, but this was 9% for infants born with orofacial clefts, and even for isolated clefts this was significantly (three times) higher than the background population. These figures are frightening, and a more realistic view is from the excellent Danish registry. Here more than 7000 children born with clefts have been registered and followed up in Denmark between 1936 and 1987. This was achieved with patient lists, and capture-recapture methods with ascertainment of 99% of liveborn cleft-affected infants without associated anomalies or syndromes. This provides a more realistic reflection of the impact of clefting on mortality and morbidity. However, the most striking observation was an increased risk of suicide in both sexes. The cause of suicide is complex, but recognition of potential risk factors could enable treatment and prevention in people born with birth anomalies. Most attention is to the early years of health in children born with congenital malformations, but as more now survive serious birth defects into adulthood, then understanding the full life course of these disorders is important to provide optimal preventive health care [24]. Large population studies are needed with genetic information coupled to environmental exposures to fully map health expectations for those born with a cleft.

There was also an increased risk associated with all major causes of death, but there was only a marginally increased mortality due to cancer among people with CLP compared with the general population, which did not support previous observations [25,26]. There is evidence from epidemiological population-based studies that birth anomalies are associated with an increased incidence of cancer [27,28]. These anomalies include nonsyndromic CL+/P, in which the evidence for increased incidence of cancers among cases and unaffected first-degree relatives is not convincing in either direction [26–29]. There are also limitations of comparing cancer incidence in nonsyndromic CL+/P cases with that in the noncleft population. Cancers are distinct, and if different types are examined in cleft populations the numbers become too small for meaningful conclusions. This is even more diluted when considering syndromic and nonsyndromic clefting, let alone the subtypes.

Although population studies have found inconsistent evidence for increased incidence of cancer in nonsyndromic CL+/P cases, there is a case for using population genetics to explore this further. A recent approach has been to examine the shared genetic etiology between nonsyndromic clefting and oral cavity/oropharyngeal cancers, which affect similar anatomic regions and may share etiological risk factors [30]. This involves Mendelian randomization being used to test the possibility that common nonsyndromic clefting genetic variants, a latent measure of an individual's underlying liability to nonsyndromic CL+/P will influence cancer risk. A similar approach has been used to provide evidence of shared genetic influences between nonsyndromic CL+/P and facial morphology [31]. Very large samples were used to estimate genetic overlap using nonsyndromic CL+/P polygenic risk scores. There was evidence for an association between nonsyndromic CL+/P polygenic risk scores and increased odds of oral cavity/oropharyngeal cancers, but there was no confirmation of an association when UK Biobank was used in a replication study. Thus, through this analysis, the major nonsyndromic CL+/P risk variants are unlikely to influence oral cavity/oropharyngeal cancers. This approach is comprehensive and would need to be used with specific other cancers and specific cleft phenotypes with very large samples and population controls.

There is, in summary, no strong evidence of an association between clefting and cancer. The indication of risk of suicide has not been replicated in the Swedish registry, which may reflect intervention strategies ameliorating this risk.

6. Education

There has been for some time evidence that children born with nonsyndromic CL+/P struggle with educational attainment [32], which can have wide adverse impacts on vocational, social, mental, and physical health outcomes [33]. This has the potential for an additional burden on a child born with cleft, and potential intervention can be invoked if we can understand the etiology. However, this is complex, because there have been suggestions of differences in brain structure or function [34], as well as compromised hearing, delayed speech development, and the potential impact of classroom bullying and social exclusion. We also know that cleft type and gender are factors; male individuals with CPO and female individuals with CLP are most vulnerable [32], and girls are more negatively affected than boys [35,36]. It is difficult to make comparisons across countries and cultures, but in most studies, those with CPO have the most negative outcomes, followed by those with CLP and CL only being the least affected. Objective educational measures and targets vary from country to country and dissection of the educational issues for those born with cleft requires more detailed studies, but all academic subjects have low attainment [36–39]. There is further impact in that birth order shows that younger siblings have higher risk of poor academic outcomes [40] with shared socioeconomic circumstances explaining some of the observed differences in academic achievement [36–39].

To start unscrambling the possible causes of this poor educational attainment, we hypothesized that common variant genetic liability with nonsyndromic CL+/P influences educational attainment. This research used methodologies similar to those described for facial morphology and cancer risk [30,31]. In summary, there was little evidence for shared genetic liability, and common genetic variants are unlikely to predispose individuals born with

nonsyndromic CL+/P to low educational attainment or intelligence, and interventions can be developed to improve their educational attainment [41].

7. Conclusion

This brief article has highlighted how orthodontists have been central to the care of children born with a cleft. Service configuration has a proven impact, and if linked with national registration and research strategy, outcomes can be demonstrated with linkage to genetic and environmental influences. Much of the research detailed throughout this article has been driven by orthodontists. The effort needed to attain these goals is considerable, but will positively influence the lives of a child born with a cleft.

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