

ORIGINAL ARTICLES

Editor's Note: In 2002 the World Health Organization published a report on the WHO meetings on International Collaborative Research on Craniofacial Anomalies. With their permission, I thought it important to share excerpts from that report with the readership of the CPCJ. An abstract introducing the report has been provided by Dr. Bill Shaw, a cochair of the meetings.

Global Strategies to Reduce the Health Care Burden of Craniofacial Anomalies: Report of WHO Meetings on International Collaborative Research on Craniofacial Anomalies

Although several significant research projects have arisen from international cooperation, especially in the field of genetics, these have been the exception rather than the rule. However, those of us who had the privilege and delight of participating in the World Health Organization meetings were struck by a common realization of the vast potential of systematic international cooperation. It is clear that the global model will be the most effective approach for tackling the big questions in craniofacial anomalies, be they concerned with cause, treatment, or prevention.

This report will serve as a road map for making collaboration the rule and not the exception and hopefully be a stimulus for the creation of partnerships between international research teams and funding agencies.

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Craniofacial anomalies (CFAs) are a highly diverse group of complex congenital anomalies. Collectively they affect a significant proportion of the global society (Table 1).

The prevalence of individual conditions varies considerably across geographic areas and ethnic groupings. Their impact on speech, hearing, appearance, and cognition has a prolonged and adverse influence on health and social integration. The costs incurred from CFAs in terms of morbidity, health care, emotional disturbance, and social and employment exclusion are considerable for affected individuals, their families, and society. Research that will increase the understanding of the causes of CFAs, improve the treatment for it, and lead ultimately to its prevention or reduction has mainly been pursued in the absence of an international strategy. Yet international collaboration is a prerequisite for accessing adequate samples for research in etiology, treatment, and prevention and also for the assembly of a critical mass of clinical researchers and basic scientists in fields such as molecular biology, genetics, biochemistry, and epidemiology.

The treatment of CFAs has, so far, escaped the rigors of

contemporary health technology assessment, and great confusion surrounds the optimal management for even the most common conditions. For each of the many subgroups of CFAs, the attainment of homogeneous samples of adequate size for randomized trials and long-term follow-up represents a formidable challenge. Multisite cooperation is essential. In the developing world, the costs of rehabilitation and problems of access put treatment beyond the reach of vast numbers of affected individuals. Systems for delivering care in different geographic and economic circumstances urgently require research.

The potential of research on the genetic basis of CFAs has increased dramatically over the last decade with the development of recombinant DNA technology. In more than 50 craniofacial syndromes, genes involved have either been mapped to a chromosome location or actively isolated and their structure identified. This achievement, however, represents only a fraction of the total number of craniofacial syndromes defined. The pathogenesis of the most common forms of CFA—non-syndromic clefts of lip, cleft palate or both—is especially challenging because they appear to arise from complex polygenic interactions with environmental factors. A coordinated international approach would not only provide effective means of sharing data, samples, and resources but also would allow strategic exploitation of geographic and ethnic variation in the incidence and pathogenesis of CFAs.

This report was based on meetings held in Geneva, Switzerland, November 5–8, 2000, and Park City, Utah, May 24–26, 2001. A complete version of the report can be obtained from the WHO by e-mailing bookorders@who.int.

TABLE 1. Examples of Most Common Craniofacial Anomalies*

<i>Anomaly</i>	<i>Prevalence at Birth per 10,000</i>
Cleft lip ± palate	
Caucasian	10
Japanese	20
Native (North) American	36
African American population	3
Cleft palate	
Averaged across races	5
Craniosynostosis	3
Crouzon syndrome	0.4
Apert syndrome	0.15
Otomandibular anomalies	1.2
Treacher Collins syndrome	0.2
CHARGE association	1
Holoprosencephaly	1.2
Stickler syndrome	1
Fetal alcohol syndrome	2

*Source: Rovin et al., 1964; Temple, 1989; Cohen et al., 1992a, 1992b; Lewanda et al., 1992; Croen et al., 1996; Derijcke et al., 1996; Sampson et al., 1997; Blake et al., 1998.

Research that may lead to the prevention of CFAs has been based primarily on isolated case-control studies in Asia, Europe, Latin America, and the United States. As yet, these projects have occurred independently of each other, and consistent conclusions about viable interventions such as dietary supplementation in the periconceptual period have yet to emerge. Once again, international standardization of research protocols, consensus on preventive interventions suitable for clinical trials, and the performance of trials in an international framework would enhance the validity, consistency, and generalizability of these efforts.

Efforts to define an international research strategy go back more than a decade when the proposals for “International Collaboration on Oral Health” were jointly published by the World Health Organization (WHO), the International Dental Federation (FDI), and the U.S. National Institute for Dental and Craniofacial Research. More recently these proposals were renewed at a series of consensus meetings:

- Eighth Congress of the International Confederation of Craniofacial Teams; Singapore; 1997.
- Craniofacial Genetic Diseases and Disorders Planning Workshop; Bethesda, Maryland; 1997.
- International Collaboration on Oral Cleft Genetics Second Meeting; Baltimore, Maryland; 1998.
- Meeting of the International Task Force on CFA; Bauru, Brazil; 1998.

In 2000, the WHO Human Genetics Program, with financial support from the United States National Institute of Dental and Craniofacial Research, launched a 5-year project designed to take forward an international research strategy on craniofacial anomalies. The specific objectives of this initiative are:

- To develop an international network for consensus building,

planning, and protocol development for international, collaborative, biomedical, epidemiological, and behavioral studies in the core areas of CFA research.

- To create a directory of CFA research resources.
- To establish a publicly accessible research database on the Internet.

As a first step of this initiative, a consensus conference of international experts covering the four selected areas for research—treatment of CFAs, gene/environment interaction (GEI), genetics, and prevention—was held under the auspices of the WHO. The conference comprised two meetings. The first, held in Geneva November 5–8, 2000, included concurrent workshops on research concerning the genetic basis of CFAs, gene/environment interactions, and the treatment of CFAs; the second, held in Utah May 24–26, 2001, considered the prevention of CFAs.

The aims and objectives of the WHO consensus meetings were to: (1) obtain counsel from experts involved in CFA research around the world; (2) describe the state-of-the-science with regard to treatment, genetics, gene/environment interaction and prevention, and highlights of recent relevant research; (3) discuss requirements for future research in all areas of craniofacial anomalies; and (4) arrive at a consensus on approaches to address data gaps and proceed with strategies, methodologies, and protocols to advance knowledge.

TREATMENT

Three interrelated research issues were addressed within the clinical theme: (1) evidence-based care (the identification and dissemination of optimal clinical interventions for the management of CFAs); (2) quality improvement (the development and dissemination of methodologies for monitoring and improving the delivery of clinical services); (3) access and availability (the identification of strategies to maximize access to adequate levels of care for all affected individuals, irrespective of nationality).

Gene/Environment Interaction

Several issues were discussed in relation to the planning of future collaborative gene/environment interaction (GEI) research.

Identification of Data Gaps

1. Use birth surveillance systems to determine the frequency of craniofacial anomalies and sources in ascertainment.
2. Identify areas of the world in which interesting populations or patterns of craniofacial anomalies exist and gain access to those populations.
3. Evaluate whether an established infrastructure exists to allow research in GEI to proceed.
4. For GEI research it will be essential to carefully categorize samples by type of defect, identify (and exclude) syn-

dromes that are known to have a genetic etiology, and, where possible, control methodological and demographic parameters that might confound biochemical and genetic analyses. This type of research is therefore predominantly applied to nonsyndromic orofacial clefts (OFCs).

5. GEI research should seek to establish the frequency of genotypes in different populations and ethnic groups and establish the risk of OFCs associated with the gene variant alone, environmental exposures alone, and gene/environment interaction.

Study Design and Standardization Issues

Having identified data gaps, appropriate research hypotheses can be generated. Agreement will be required on the data to be collected, the methods of sample collection, and the geographical areas in which research would be carried out. In time it would be anticipated that the research would address the data gaps identified and raise further issues that would be addressed by generating further hypotheses to be tested in a cycle of enquiry and research.

Common Core Protocols

It was agreed that the standardization of research would require the development of guidelines to provide consistency between groups collecting data. Such common core protocols would be developed in the area of: (1) nutritional, lifestyle, and occupational factors; (2) medical, obstetric, and drug histories; (3) genetic and biochemical data collection; (4) assessment of clinical dysmorphology and collection of consistent family history data; and (5) agreed guidelines for ascertainment of cases and, where appropriate, controls.

Genetics

Although there is an inevitable overlap between research in genetics and gene/environment interaction, CFA research will benefit from an intensive genetics approach.

The discussions on the genetics component of the WHO CFA conference focused on those technologies, analytic approaches, and populations that will best advance our understanding of the etiologies of craniofacial abnormalities, with particular reference to those with strong genetic components.

Although recognizing that the environment and stochastic events play an important and often major role in predisposing to craniofacial anomalies, the role of genetics is compelling in many situations.

Funding, manpower training, and bioethical and government policy issues also influence research. These should be discussed and addressed in light of identified differences in the demographics and infrastructure in different regions, and research priorities should be established geographically and according to agreed criteria.

Prevention

1. Identify environmental and behavioral factors with established associations with OFCs and other CFAs.
2. Review evidence on the role of specific maternal nutritional factors in the etiology of OFCs and other CFAs.
3. Reach a consensus regarding the role and importance of nutritional supplementation trials in evaluating the causal role of specific nutrients in the etiology of OFCs and other CFAs.
4. Discuss aspects of the design of OFC and CFA prevention trials and their ethical, legal, social, and financial implications.
5. Make recommendations on the resources needed to implement international collaborative studies of CFA prevention with common core protocols.

The following section provides details of the recommendations for future research arising out of the two WHO consensus meetings.

CONCLUSIONS AND RECOMMENDATIONS

After thorough discussions of the many initial options, the following major themes were proposed.

Treatment of CFAs

Three interrelated research issues were addressed within the clinical theme.

Evidence-Based Care

This issue focuses on the replacement of current widespread uncertainty and confusion in clinical care with a sound evidence base derived from rigorous clinical research.

There is a pressing need to mobilize a critical mass of clinical research expertise and access sufficiently large samples of patients for adequately powered clinical trials. Initial efforts should include the following:

1. Trials of surgical methods for the repair of different OFC subtypes, not just unilateral clefts.
2. Trials of surgical methods for the correction of velopharyngeal insufficiency.
3. Trials of the use of prophylactic ventilation tubes (grommets) for middle-ear disease in patients with cleft palate.
4. Trials of adjunctive procedures in cleft care, especially those that place an increased burden on the patient, family, or medical services, such as presurgical orthopedics, primary dentition, orthodontics, and maxillary protraction.
5. Trials of methods for the management of perioperative pain, swelling and infection, and nursing.
6. Trials of methods to optimize feeding before and after surgery.
7. Trials addressing the special circumstances of care in the

developing world in respect of surgical, anesthetic and nursing care.

8. Trials of different modalities of speech therapy, orthodontic treatment, and counseling.

Equally urgent is the need to create collaborative groups, or improve the networking of existing groups, to develop and standardize outcome measures. There is an especially urgent need for work on psychological and quality-of-life measures and economic outcomes.

For rare interventions, prospective registries should be established to hasten collaborative monitoring and critical appraisal, equivalent to phase I trials. Relevant topics would be craniosynostosis surgery, ear reconstruction, distraction osteogenesis for hemifacial macrosomia and other skeletal variations, midface surgery in craniofacial dysostosis, and correction of hypertelorism.

Quality Improvement

Quality improvement focuses on the development and dissemination of methodologies for monitoring and improving the delivery of clinical services.

The international adoption of a set guideline for the provision of clinical services and the maintenance and analysis of minimum clinical records of cleft care is proposed. Various registries of clinical outcomes have recently emerged and are working independently. Efforts should be made to harmonize these registries.

Access and Availability

Strategies to maximize access to adequate levels of care for all affected individuals, irrespective of nationality must be identified.

In large parts of the world, routine public health services are unable to afford treatment for CFAs. Three general approaches can be identified: high volume indigenous centers of excellence; contracts between nongovernmental organizations (NGOs) and local hospitals; and volunteer short-term surgical missions. The long-term benefit of these efforts could be developed by the following:

- A survey of the charitable organizations involved and the scale of their work.
- An appraisal of the cost-effectiveness and clinical effectiveness of the different models of aid.
- The promotion of dialogue between different NGOs to develop commonly agreed codes of practice and adoption of the most appropriate forms of aid for local circumstances, with an emphasis on support that favors indigenous long-term solutions.
- The initiation of clinical trials concerning the specifics of surgery in a developing country setting, one-stage operations, optimal late primary surgery, anesthesia protocols (e.g., local anesthetic, inhalation sedation), and antisepsis.

- The development of common core protocols for genetic, epidemiological, and nutritional studies alongside surgery.

Gene/Environment Interaction

Epidemiology

The overall conclusions to be drawn from the data presented are as follows:

- There is ample evidence of the distinctly different nature of cleft lip and palate (CL/P) and cleft palate (CP), and emerging evidence of distinct differences in subgroups within these overall conditions.
- There is a great deal of geographical variation, which is more apparent for CL/P than CP.
- There is considerable variation in the proportion of cases of OFCs with additional congenital anomalies and syndromes.
- It is evident that migrant groups retain rates of CL/P similar to those of their area of origin.
- There is no consistent evidence of time trends and no consistent variation by socioeconomic status or seasonality, but neither of these aspects has been adequately studied.
- There is considerable international variation in the frequency of OFCs, but validity and comparability of data are adversely affected by numerous factors, among which are: (1) source population of births considered (hospital versus population), (2) time period, (3) method of ascertainment, (4) inclusion/exclusion criteria, and (5) sampling fluctuation.
- There are many parts of the world in which we have little or no information on the frequency of OFCs, in particular parts of Africa, Central Asia, Eastern Europe, Middle East, and Russia.

Etiology

The following points are relevant:

- There are multiple genes involved in OFCs.
- Analysis should be separated for cleft lip, cleft lip and palate, and cleft palate because cleft lip and palate is not the same as cleft lip only.
- Heterogeneity should be expected, and therefore different populations will need to be examined for validation of a result.
- Nutrition remains an eligible area for research, and the roles of folic acid and multivitamins, including folic acid, vitamins A, B₂, B₆, and B₁₂, as well as zinc, need further investigation.
- Smoking, alcohol, epilepsy, certain medications, and environmental factors may explain a small but appreciable portion of birth defects.
- Main gaps in knowledge are examination of coteratogens and gene/environment interaction (e.g., with alcohol are there co-teratogens, such as folate deficiency) and is there a threshold beneath which alcohol is safe?

It is important to be able to differentiate the exposure and the genetic predisposition and identify those at risk to allow selective counseling because general advice regarding alcohol and smoking in relation to disease is not easy to impart in attempting to achieve changes in behavior.

One major issue in the reporting of associations with exposures is the distinct possibility of publication bias in the literature.

WHO Aims and Objectives for Gene/Environment Interaction Research

The ultimate humanitarian and scientific research objective in CFA birth defects is primary prevention.

The WHO project aims to:

- Provide support for planning and development of research protocols that will advance understanding of etiology and inform future prevention initiatives.
- Facilitate Internet-based research databases.
- Support gene/environment interaction studies with international standardization of research protocols to inform the design of future efforts toward primary prevention.

These objectives can be achieved by the reinforcement of existing research collaborations and the setting up of new research collaborations.

Future Research Challenges

With the availability of the human genome sequence, researchers have increasing opportunities to study the role of genes and GEI in human health and disease. Such opportunities come with major challenges, in three main areas. The first area relates to data: to identify and, if possible, rank the major data gaps separating our current knowledge from that needed for clinical and public health action. The second area relates to methods: how to conduct, analyze, and present studies of multiple genetic and environmental factors in ways that efficiently fill the data gaps. The third area relates to people and institutions: how to learn more and more quickly using the unique opportunities inherent in international collaboration.

Common core protocols for data collection and further studies into research methodology to compare various data analysis models are urgently required.

Genetics

The focus of the genetics component of the WHO Craniofacial Conference was on discussing those technologies, analytic approaches, and populations that will best move us forward toward a better understanding of the etiologies of craniofacial abnormalities with particular reference to those that have strong genetic components. Although recognizing that the environment and stochastic events play an important and often

major role in predisposing to craniofacial anomalies, in many situations the role of genetics is compelling.

Phenotype/Genotype Correlation

- A number of specific single-gene disorders with recognizable Mendelian inheritance, including some holoprosencephaly and craniosynostosis syndromes, serve as benchmarks for ways in which gene identification can proceed from clinical description and family-based studies through traditional cloning and functional analysis.
- The definition of a nonsyndromic cleft lip and palate remains ambiguous, and new gene discoveries leading to improvements in genetic diagnoses will potentially improve sensitivity and specificity of genotype-phenotype correlation.
- There is some emerging evidence that traditional separations between cleft lip, with or without cleft palate, and cleft palate only may be breaking down, and further work in this area is essential.
- It is therefore important in research to be able to subphenotype cases of children whose abnormalities are limited to clefts or clefts and one additional abnormality. Clinical descriptors that will allow breaking this group down into finer detail will be particularly important in facilitating genetic analysis.

Analytical Methodologies

- Technological and analytic approaches will include new methodologies for genotyping, the strategy by which markers will be chosen for genotyping, and the selection of candidate genes when that approach is being utilized.
- The strengths and weaknesses of traditional linkage approaches versus affected pedigree-member approaches and transmission disequilibrium testing (TDT) and linkage disequilibrium were also developed.
- The strengths of these approaches often overlap and combinatorial approaches using candidate genes in conjunction with affected pedigree-member linkage and TDT can all be carried out in parallel with one another.

Collection and Storage of Genetic Data

- Analysis is driven by sample collection, and there are both strengths and weaknesses in rapid, cost-efficient, and small-amount sample collection, as is exemplified by blood spots or cheek swabs; and whole blood or cell line collections that would allow for more extensive analysis of protein and RNA.
- International collaboration is essential in that etiologies are likely to be diverse across populations but with some underlying gene and environmental causes shared in common.
- Multicenter collaborations afford the opportunity for the collection of large numbers of samples to have sufficient power to confirm linkage or association studies; there are a number of active ongoing collaborations.

Parallel Research and Multidisciplinary Approach

- The role of animal models and the insights gained from developmental biology into choosing both genes and pathways involved in CFA genetics have never been more apparent than they are now.
- It will be through the interactive efforts of clinicians, epidemiologists, statisticians, molecular biologists, and developmental biologists that we will make our most rapid progress.

Role of WHO

In the ongoing efforts to globalize CFA research, the WHO group will coordinate work on outlining candidate genes, markers, analytic approaches, and animal models of use and will streamline efforts toward establishing collaborative groups to establish a set of protocols and guidelines for future efforts in this area.

Prevention

Primary Prevention

Orofacial clefts appear to have substantial environmental causes; the potential for their occurrence thus seems considerable. The pattern of occurrence of OFCs is different from that of neural tube defects so their causes may also be different.

- Maternal tobacco use has been consistently associated with a modest elevation in risk of OFCs, but the attributable risk may be of public health importance. Moreover, tobacco use is rapidly increasing among women, especially in technologically developing countries, and many women are exposed to passive smoking in the home and workplace.
- Maternal alcohol use, well known as a cause of the fetal alcohol syndrome, has also been associated with risk of isolated OFCs in some, but not all, studies. The type and context of alcohol consumption differs considerably across populations, and more consistent methods are needed for the assessment of maternal alcohol intake. The possible increased risk of OFCs and other CFA related to the common exposures of smoking and alcohol use during pregnancy is a message that should be incorporated into health promotion programs for women of reproductive age.
- Maternal nutritional factors have been associated with the risk for OFCs in human population studies, although strong evidence of a causal relationship is still lacking. The most promising candidate nutrients include folic acid and pyridoxine (vitamin B₆), and some evidence also exists of possible roles for riboflavin (vitamin B₂) and vitamin A.

Intervention Trials

The current state of equipoise regarding maternal nutrition and OFCs makes intervention trials of specific nutrients an urgent priority. The proven intervention of folic acid supplements in the prevention of occurrence of neural tube defects must also be acknowledged in the design of prevention trials involving folic acid. No single trial is likely to be definitive, and trials are needed in diverse populations in both industrialized and technologically developing countries. Trials in high-risk populations are more likely to detect a treatment effect than trials in low-risk populations and at lower cost and with greater speed.

Choice of Nutrient

The choice of specific nutrient interventions should be based on prior detailed studies of biochemical indicators of nutritional status in the population of interest, and all prevention trials should adhere to current ethical and methodological standards. Poorly conceived and conducted trials are unethical because they waste limited resources and add further delay to discovering effective interventions.

Recurrence Trial

An OFC recurrence-prevention trial is far more feasible than a trial of prevention of primary occurrence but would still require many thousands of high-risk mothers. OFC surveillance systems and registries in countries around the world need to be further developed and linked to provide the critical infrastructure for OFC prevention trials.

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