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Conference Report

Priorities for Public Health Research on Craniosynostosis: Summary and Recommendations From a Centers for Disease Control and Prevention-Sponsored Meeting

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On June 8–9, 2006, the National Center on Birth Defects and Developmental Disabilities at the Centers for Disease Control and Prevention held a meeting entitled "Prioritizing a Public Health Research Agenda for Craniosynostosis". The meeting goals were to review current knowledge in the area, discuss research gaps, and identify future priorities for public health research. Participants with a broad range of expertise (including clinical and molecular genetics, cranial morphology, epidemiology, pediatrics, psychology, public health, and surgery) contributed to the development of the research agenda. Meeting participants were asked to consider public health significance and feasibility when identifying areas of priority for future public health research. Participants identified several priorities, including the need to better delineate the prevalence and phenotype of craniosynostosis (CS); to identify factors important in the causation of CS (including potentially modifiable environmental risk factors as well as genes involved in isolated CS and gene–gene and gene–environment interactions); and to better understand short- and long-term outcomes of CS (e.g., surgical, neurocognitive and neuropsychological outcomes, psychological adjustment, and social relationships) and issues related to clinical care that could affect those outcomes. The need for improved collaboration among clinical treatment centers and standardization of data collection to address these priorities was emphasized. These priorities will be used to guide future public health research on CS. Published 2007 Wiley-Liss, Inc.†

Key words: cranial suture; epidemiology; public health; surgery; psychology; genetics; research priorities

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INTRODUCTION

On June 8–9, 2006, the National Center on Birth Defects and Developmental Disabilities at the Centers for Disease Control and Prevention (CDC) sponsored a meeting on craniosynostosis (CS), entitled "Prioritizing a Public Health Research Agenda for Craniosynostosis" to identify priorities for public health research on this defect. The 29 meeting attendees covered a broad range in expertise, including clinical and molecular genetics, cranial morphology, epidemiology, pediatrics, psychology, public health, surgery, and other areas.

The meeting began with a review of the current state of knowledge in several research areas, including genetic and environmental risk factors and gene–environment interaction, surgery for CS (techniques, timing, and impact on various outcomes), and neurocognitive and psychosocial outcomes. After these presentations, attendees were divided into two breakout groups, covering major areas of public

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health research in CS: (1) genetic and environmental risk factors and gene–environment interaction in the causation of CS, and (2) secondary outcomes (short- and long-term), such as surgical results, and neurocognitive and psychosocial outcomes. Each group defined key research areas and identified research gaps and areas of priority based on public health significance and feasibility. The two groups subsequently reconvened and created a comprehensive public health research agenda. This agenda will be used to help guide future public health-related CS research.

REVIEW OF CURRENT KNOWLEDGE

Several experts presented reviews of the current state of knowledge about CS and identified gaps, which laid the groundwork for the remainder of the meeting. Highlights of the presentations are summarized here.

Dr. M. Michael Cohen Jr., Dalhousie University, Halifax, Nova Scotia, provided an overview of CS [Cohen, 2005]. CS is defined as premature fusion of one or more cranial sutures, the fibrous connections between adjacent intramembranously formed bones. These sutures allow passage of the head through the birth canal, serve as shock absorbers and permit the rapid brain growth that occurs early in life. Of the four major cranial sutures, the sagittal, coronal, and lambdoid sutures typically close in the third decade of life. In contrast, the metopic suture typically closes by 8 months of age [Weinzweig et al., 2003], although it fails to fuse in approximately 10% of the general population.

CS often results in an abnormal head shape. The observed head shape (e.g., scaphocephaly, plagiocephaly, etc.) is dependent on the specific sutures that close prematurely and the timing and order of premature closure. Of note, posterior plagiocephaly, which can occasionally occur secondary to unilateral lambdoid suture fusion, is most often caused by external mechanical forces (deformation) without premature suture closure. Distinguishing synostotic and deformational posterior plagiocephaly may sometimes be challenging [Huang et al., 1996], although clinical evaluation of skull shape by an expert together with a three-dimensional CT study is almost always diagnostic. In addition to an abnormal head shape, other complications can also occur, including problems with vision and hearing [Khan et al., 2003; Church et al., 2007].

Population-based estimates suggest that the birth prevalence ranges from 3.1 to 4.8/10,000 live births [French et al., 1990; Lajeunie et al., 1995]. In descending order, isolated CS involves the sagittal, coronal, multiple sutures, metopic and lambdoid sutures [Anderson and Geiger, 1965; Shillito and Matson, 1968; Hunter and Rudd, 1976, 1977; Lajeunie et al., 1995, 1996, 1998]. CS has been associated with over 100 syndromes [Online Mendelian Inheritance in Man, 2007]. In contrast to isolated CS, the sutures most commonly involved in CS associated with known syndromes (termed "syndromic") differ from those involved in isolated cases (e.g., coronal sutures are more commonly involved in CS due to various mutations).

Isolated and syndromic CS can be simple (with a single suture-type involved) or complex (more than one suture-type involved); complex CS accounts for about 5% of isolated CS [Chumas et al., 1997]. As the number of fused sutures increase, the risks of elevated intracranial pressure and cognitive impairment also increase. The pathogenesis of CS can be primary (premature suture obliteration in the absence of extrinsic factors) or secondary to other abnormalities [Cohen, 2005]. Some causes of secondary CS include metabolic disorders (e.g., hyperthyroidism), mucopolysaccharidoses, brain malformations (e.g., holoprosencephaly), hematologic disorders (e.g., thalassemias), and shunted hydrocephalus [Roberts and Rickham, 1970; Cohen, 2005].

Dr. Andrew Wilkie, University of Oxford, Oxford, UK, reviewed genetic risk factors for CS. Mutations of fibroblast growth factor receptor genes have been seen in patients with CS, including mutations in *FGFR1* in Pfeiffer syndrome; *FGFR2* in Apert, Pfeiffer, Crouzon, and Beare-Stevenson syndromes, and in isolated coronal CS; and *FGFR3* in Muenke syndrome and Crouzon syndrome with acanthosis nigricans. Mutations in other genes are seen in Saethre-Chotzen syndrome (*TWIST1*), Boston CS (*MSX2*), Antley-Bixler syndrome (*POR*), craniofrontonasal syndrome (*EFNB1*), Carpenter syndrome (*RAB23*), and isolated coronal synostosis (*EFNA4*) [Merrill et al., 2006; Wilkie et al., 2006; Jenkins et al., 2007]. Although these single-gene conditions appear to account for about 25% of CS [Morriss-Kay and Wilkie, 2005], most cases of CS are likely caused by a combination of genetic and environmental factors.

The contribution of single-gene mutations to the phenotype in persons with CS depends on the genetic mutation identified. For example, the observed phenotype associated with Apert syndrome is primarily due to the *FGFR2* mutation, although other genes and environmental factors play a lesser role [Slaney et al., 1996]. The Muenke syndrome phenotype also has a strong genetic component, related to mutation in *FGFR3*, but more of the observed variation is due to other genes and environmental factors. In contrast, several gene mutations with lower penetrance have been identified, in which the specific gene mutation predisposes to a phenotype, but other unidentified factors play a critical role [Johnson et al., 2000; Funato et al., 2005; Wilkie et al., 2006].

Recent reports have emphasized the importance of identifying a molecular genetic diagnosis, when possible, in studies of CS. Molecular genetic testing

is helpful in establishing a diagnosis and recurrence risks, but it can also be predictive of the need for early surgery or repeat surgery and of cognitive prognosis [Johnson et al., 1998; Thomas et al., 2005; Wilkie et al., 2006]. Incorporating information on molecular diagnosis in future studies of CS should help elucidate the prognostic value of these factors.

Dr. Wilkie raised several important questions. These included (1) how to incorporate information on reduced-penetrance mutations into routine diagnostic services, given that the other factors involved are not currently well understood [Merrill et al., 2006]; (2) whether polygenes can be identified in isolated CS and what value this information would have; (3) whether further monogenic risk factors with predictable phenotypes can be identified; (4) whether isolated cases with a high genetic load can be reliably distinguished from polygenic or environmental phenocopies; and (5) what recurrence risk figures should be used for genetic counseling for isolated CS, given that data used to develop these estimates [Carter et al., 1982] were unable to incorporate molecular testing. Other issues raised by Dr. Wilkie included the mechanism by which different types of cranial sutures vary in their predisposition to CS, the interaction between genes and regulatory networks with biomechanical strain, and the ability of studies of right-sided predominance of coronal CS to provide insight into its pathogenesis.

Dr. Suzan Carmichael, California Birth Defects Monitoring Program, Berkeley, CA, focused on environmental risk factors for CS and potential gene–environment interactions. Several potential environmental risk factors have been examined, but in most cases, the factor has not been identified definitively to be associated with CS. Infant sex is a recognized risk factor for CS, with males affected more often with sagittal CS [Alderman et al., 1988; Kallen, 1999; Zeiger et al., 2002] and females affected more often with coronal CS [Lajeunie et al., 1995; Kallen, 1999]. Other environmental risk factors have been less well studied. White race was associated with CS in two studies [Alderman et al., 1988; Reefhuis et al., 2003]. Two studies have shown an association between increased paternal age and CS [Alderman et al., 1988; Singer et al., 1999]. Whether this age-related association is due to unrecognized single-gene mutation is unknown. In another study, certain parental occupations were associated with CS [Bradley et al., 1995]. One often-hypothesized cause, fetal head constraint, is difficult to study in humans, given the absence of an objective measure, but animal studies have provided some support for this hypothesis [Koskinen-Moffett et al., 1982]. Epidemiologic data on whether intrauterine constraint is a risk factor is limited; one study showed an association between breech delivery and CS, but the effect was not statistically significant [Singer et al., 1999].

Limited data suggest that maternal use of certain classes of medications, anticonvulsant (in particular, valproic acid) [Kallen and Robert-Gnansia, 2005], nitrosatable [Olshan and Faustman, 1989; Gardner et al., 1998; Kallen and Robert-Gnansia, 2005], and thyroid medications [Gardner et al., 1998; Rasmussen et al., 2007] could be associated with an increased risk of CS. Whether maternal nutrition plays a role in causation of CS is unknown; in one study, no association was observed between maternal use of multivitamin supplements and sagittal CS [Zeiger et al., 2002], while another study suggested the possibility of an increased risk of CS associated with first trimester folic acid exposure, but these findings were not statistically significant [Kallen and Robert-Gnansia, 2005]. For several other factors, the results of different studies have been conflicting. These include parental education [Alderman et al., 1988; Kallen, 1999; Zeiger et al., 2002; Reefhuis et al., 2003], advanced maternal age [Kallen, 1999; Singer et al., 1999; Reefhuis et al., 2003; Reefhuis and Honein, 2004; Kallen and Robert-Gnansia, 2005], parity [Alderman et al., 1988; Kallen, 1999; Reefhuis et al., 2003; Kallen and Robert-Gnansia, 2005], plurality [Alderman et al., 1988; Singer et al., 1999; Reefhuis et al., 2003], fertility treatments or sub-fertility [Reefhuis et al., 2003; Kallen and Robert-Gnansia, 2005], maternal cigarette smoking [Alderman et al., 1994; Kallen, 1999; Honein and Rasmussen, 2000; Zeiger et al., 2002; Reefhuis et al., 2003; Kallen and Robert-Gnansia, 2005], alcohol consumption [Alderman et al., 1994; Zeiger et al., 2002], and increased altitude [Alderman et al., 1988, 1994].

Previous studies have often been plagued by serious methodological limitations, including inconsistent case ascertainment and inclusion criteria, limited information on exposure timing, variable phenotype-specific analyses, and lack of adjustment for potential confounding factors. These limitations may have contributed to the lack of consistency in findings on CS risk factors. Future studies will require population-based data sources to diminish the bias resulting from use of clinical data sources and to increase the ability to generalize the results.

Most genetic studies have been limited to syndromic cases, although the majority of CS cases are isolated. The genetics of isolated cases has been relatively unexplored [Seto et al., 2007], and limited data are available on gene–environment interaction. One possible non-genetic factor that has been hypothesized to interact with gene mutations is intrauterine constraint. A case report of a patient with unicoronal CS with an Ala315Ser mutation in *FGFR2* and persistent breech presentation [Johnson et al., 2000] suggests that investigation of the interaction between intrauterine constraint and genetic factors for CS might be fruitful.

Several possible unifying mechanisms in the causation of CS should be considered in the study

of gene–environment interactions, including the relationships between activation of fibroblast growth factor receptors and environmental risk factors (e.g., smoking), between altered neural crest cell migration and the interaction with folate, and between genetic risk factors and hypoxia. Other important areas for consideration are the link between infant sex and genes, and the impact of paternal age on the risk for CS.

Drs. Richard Hopper from Children's Hospital and Regional Medical Center, Seattle, WA, and Mark Urata from Children's Hospital Los Angeles, Los Angeles, CA, discussed surgical treatment for single-suture and multiple-suture CS, respectively. Their presentations focused on three issues: (1) indications for surgical treatment, (2) surgical techniques used, and (3) age at which surgery should take place. The reasons cited for surgical treatment can vary and range from relieving increased intracranial pressure to optimizing neurocognitive and psychosocial outcomes, to correcting the disfiguring effects of CS [Mouradian, 1998; Renier et al., 2000; Netherway et al., 2005; Anderson et al., 2007]. Increased intracranial pressure is found most often among patients with multiple-suture CS, but has also been occasionally observed among infants with single-suture CS [Camfield et al., 2000]. Evidence of increased intracranial pressure can include "soft" signs (e.g., headaches, nausea and vomiting, photophobia, and developmental delay) and "hard" signs (e.g., papilledema, CT findings, or measurement with an intracranial pressure monitoring device) [Gault et al., 1992; Tuite et al., 1996a,b].

Several approaches are available for surgical treatment of single-suture CS, including open strip craniectomy [Maugans et al., 1997], calvarial vault remodeling, spring-mediated cranioplasty [David et al., 2004], and endoscopic-assisted strip craniectomy followed by postoperative helmet molding therapy [Jimenez et al., 2002]. The surgical approach used in an individual patient can depend on the suture(s) involved, the age at diagnosis, and surgical judgment. For example, an infant with sagittal CS diagnosed at < 3 months of age might be treated with a strip craniectomy, whereas a child diagnosed at 4–9 months might have a modified Pi procedure [Boulos et al., 2004], and a child diagnosed at 1 year of age or older might be treated with total vault remodeling. In addition to age at diagnosis and suture(s) involved, the surgeon must weigh the need for early surgery to avoid further progression against operating later to minimize the chance of relapse or re-operation.

Surgical correction of multiple-suture CS is more complex than that of single-suture CS and often requires multiple procedures. The primary surgical procedure used is fronto-orbital advancement and calvarial vault remodeling, typically performed in the first year of life. Secondary procedures are frequently required and include monobloc and/or facial bipartition, LeFort III osteotomy, LeFort I osteotomy, and other procedures to achieve improved form and function. The frequency of perioperative and postoperative complications is higher among patients with multiple-suture CS than among those with single-suture CS [McCarthy et al., 1995a,b].

To optimize outcomes, surgical correction of CS is typically performed in the context of a craniofacial center using a multidisciplinary team approach. The great variation in treatment options and lack of standardized methods for comparison make it challenging to compare results from different surgical procedures [Sloan et al., 1997].

Dr. Kathleen Kapp-Simon, Northwestern University, Chicago, IL, discussed neurocognitive outcomes among children with CS, with a particular focus on perspectives of global intelligence and neuropsychological processing. Intelligence is generally within normal range in children with single-suture CS [Kapp-Simon, 1998; Speltz et al., 2004]. However learning disabilities are present in 35–50% of children with single-suture CS compared to 2–10% of the general population. These learning disabilities affect one or more neuropsychological processing skills, such as language, phonological processing, executive function, working memory, attention, visual perception, motor coordination, processing speed, and academic achievement [Kapp-Simon, 1998; Becker et al., 2005]. No association between the synostotic suture and the type or degree of global functioning impairment have been identified [Kapp-Simon, 1998; Magge et al., 2002; Shipster et al., 2003; Becker et al., 2005].

The relationship between CS and neurodevelopment is not fully understood. The two leading hypotheses are that (1) CS causes functional deficits by triggering increased intracranial pressure, secondary brain deformation, and cortical and subcortical changes; or (2) these abnormalities are the consequence of primary neuropathology [Renier et al., 1982; Speltz et al., 2004; Aldridge et al., 2005a,b]. Given the observed heterogeneity in causes of CS, it is possible that both hypotheses could be relevant in some cases. In an effort to elucidate this relationship, investigators have studied children before and after cranial vault surgery and examined the correlation between age of surgery and cognitive development [Starr et al., 2007]. However, reports on the neuropsychological outcome in children with single-suture CS following early or late cranial vault surgery versus no surgery are contradictory, and most studies have not included an adequate control population [Speltz et al., 2004; Mathijssen et al., 2006; Kapp-Simon et al., 2007].

Using neuroimaging techniques (CTs and MRIs), investigators have identified structural abnormalities in the brains of children with single-suture CS. These abnormalities include distention of the frontal

subdural space, abnormalities of the corpus callosum, small frontal lobes, wide precentral sulci, and Chiari malformation [Singer et al., 1999; Marsh, 2000]. In addition, MRI brain imaging in children with single-suture CS has demonstrated cortical and subcortical abnormalities in areas not anatomically related to the site of the fused suture [Aldridge et al., 2005a,b], as well as developmentally based correlations between brain and skull dysmorphologies [Richtsmeier et al., 2006].

Future investigations must better describe neurocognitive phenotypes among children with CS and study their associations with specific synostosed suture(s). It will also be important to determine if a relationship between these profiles and the severity or degree of variation seen in CS phenotypes exists. Finally, mutations identified either as causal or as associated with single-suture CS need to be further characterized and correlated with the neurocognitive phenotypes.

Dr. Mary Michaeleen Cradock, St. Louis Children's Hospital, St. Louis, MO, reviewed the emotional and behavioral adjustment of children with CS, the impact of CS on the family, and the interaction between the adjustment of the child and of the family. To the extent that children with CS exhibit brain abnormalities and learning disabilities, these abnormalities may interfere with normal psychosocial adaptation, affecting skills critical for behavioral control, social success, and emotional regulation.

Perceived vulnerability of the child, stigma related to the child's appearance, reduced social acceptance of the child, multiple medical procedures, and long, recurrent evaluations all can be sources of stress for the family. Compared with mothers of healthy children matched for age and socioeconomic status, mothers of children with craniofacial anomalies (including cleft lip and palate, cleft palate only, and sagittal CS) reported higher levels of stress, lower self-competence scores, and a higher degree of marital conflict in one study [Speltz et al., 1990].

Small studies do not demonstrate that cranial vault remodeling affects behavior in children with isolated CS. For example, in a study of 18 children undergoing cranioplasty during the first year of life, behavior did not differ significantly from a control group [Virtanen et al., 1999]. In a study of 30 untreated patients with single-suture CS, most of the scores on a child behavior checklist were in the average range, although there was a trend for elevated scores for internalizing problems, such as for mood disorders, attention problems, and social withdrawal [Boltshauser et al., 2003].

The impact of the family environment on the child's behavioral development has also been studied. Several authors, studying children with chronic diseases and craniofacial anomalies, have identified parental stress as one of the strongest predictors of child behavioral functioning and adjustment [Krueckeberg and Kapp-Simon, 1993; Goldberg et al., 1997; Pope et al., 2005]. However, information on self-concept and family environmental risk factors in children with single-suture CS is very limited.

PRIORITIES FOR PUBLIC HEALTH RESEARCH ON CS

Participants identified a total of 15 topics for further research. The following is a list of the topics in order of priority, beginning with the research area that received the most support from participants. In creating these priorities, the participants felt that certain issues needed to be considered, including limitations of data collection within individual treatment centers, the barriers to data sharing among centers, the need for standardization of data collection to improve comparability among centers, the existence of well-validated data-sharing protocols that could inform CS data collection (e.g., pediatric oncology protocols) [Liu et al., 2003], and the differences in multidisciplinary team care versus non-team care settings.

Better Understanding of Prevalence, Phenotype, and Genotype of CS

There is a need to better understand the prevalence, phenotype, and genotype of CS. To advance our understanding of CS and develop consistent data collection across research and clinical sites, standardized diagnostic methods for CS are needed. Developing such methods requires identification of the types of genetic evaluation and radiographic imaging needed for diagnosis, information on the appropriate specialists and timing of referrals needed for optimal diagnosis and management, and a better understanding of the role of anthropometric measures in the diagnosis of CS. Additional information is also needed on the prevalence of CS by race and ethnicity, parental age, and gestational age to better define the descriptive epidemiology of this disorder. The prevalence of specific genotypes (e.g., *FGFR3* P250R) in isolated and syndromic cases of CS should also be described. Population-based epidemiologic studies are needed to decrease bias that can be introduced through hospital- or clinic-based studies and to increase the ability to generalize results to the general population.

Identification of Environmental Risk Factors Associated With CS

Although a number of potential risk factors have been identified for CS, additional research is needed to better understand their role, especially for those that are modifiable. Risk factors of particular interest are smoking and alcohol consumption during

pregnancy, altitude of maternal residence, maternal thyroid disease, use of medications during pregnancy (e.g., valproic acid, nitrosatable medications), antacid use, infertility (including polycystic ovary syndrome), maternal obesity, and maternal diabetes. Future research should be based on population-based epidemiological studies with a diverse population to improve the ability to generalize study results.

Improved Knowledge of Neurocognitive Outcomes and Neuropsychological Issues in CS

Knowledge about the relationship between CS and cognitive impairment or difficulties in neuropsychological processing is incomplete. In addition, it is not known whether the timing or type of surgery for CS affects these cognitive outcomes. Research in this area is critical to better inform families about the long-term prognosis for children with surgically corrected CS and for children without surgical correction. Because neurocognitive and neuropsychological outcomes might vary by the cranial suture-type involved and by the particular surgical technique used, it was suggested that studies stratify by suture-type and surgical technique to better understand the outcomes for different procedures.

Characterization of the Morbidity and Mortality Associated With CS and Its Treatment

There is currently insufficient information defining the morbidity and mortality associated with cranial vault surgery among infants and children with isolated CS involving a single suture. Standardized measures are needed on how best to assess the severity of the child's phenotype before and after surgery, as well as an objective measure of facial outcomes. It is important to determine if outcomes vary by surgeon and center and by source of care (craniofacial team vs. non-team care). Studies should also address the frequency of surgical complications (e.g., extended inpatient stay, excessive blood loss) and the need for repeat surgeries.

Identification of Genetic Risk Factors for Isolated CS

More data are needed on the role of genetic risk factors in isolated CS. Approaches that could be used to better understand genes associated with CS include pedigree-based linkage studies, association studies involving a candidate gene approach, genome-wide association studies, transmission disequilibrium tests, whole genome sequencing, and gene dosage studies. Identification of the critical genes for CS could help define the studies of gene–environment interactions that should be of high priority to guide development of appropriate interventions to prevent the occurrence of CS. In addition, little is known about interactions between genes in CS. To help clarify the role of gene–gene interactions, animal models and population-based epidemiologic studies are needed.

Understanding the Role of Intrauterine Constraint in CS Causation

The role of intrauterine constraint in the development of CS is still not clear. Factors potentially contributing to intrauterine constraint include multiple gestation, mode of delivery, maternal uterine abnormalities, orientation of head during late gestation, oligohydramnios, primigravity, umbilical cord length, gestational age, and infant's size at birth related to maternal size. Epidemiological studies are needed to determine whether these factors are associated with the occurrence of isolated CS.

Investigation of Gene–Environment Interaction

There has as yet been no population-based investigation of possible gene–environment interactions in the causation of CS. Identification of gene–environment interactions will provide opportunities for interventions to reduce the risk of CS among persons with a genetic risk factor for the condition. Studies should be designed to consider whether gene–environment interactions differ by CS type (isolated, syndromic, and non-syndromic associated with other defects) and by type of suture affected. Animal models and population-based epidemiological studies could help to further our understanding of gene–environment interactions.

Improved Diagnosis and Ascertainment of CS

It is not known whether outcomes for children with CS are improved by early diagnosis, referral, and treatment. Information is needed on the age at diagnosis of CS among children with isolated CS and on its impact on outcome. Another issue important for research in CS is related to ascertainment of children with CS. Ascertainment by population-based birth defects surveillance systems can be challenging because of several factors, including delay in diagnosis, variations in diagnostic methods, and treatment in outpatient settings that are not typically used as surveillance sources. This issue will need to be addressed to improve the quality of epidemiologic studies of CS.

Understanding Long-Term Outcomes in CS

The majority of CS treatment occurs relatively early, and typically no long-term follow-up of uncomplicated cases is performed by the craniofacial team who provided initial care. Information is needed on

longer-term outcomes for adolescents and adults who have undergone surgical treatment of CS, including data on neurocognition, possible barriers to employment, mental health and reproductive issues, and potential sources of excess morbidity and mortality, including mortality from causes presumed to be unrelated (e.g., cancer), as has been hypothesized for orofacial clefts [Bille et al., 2005].

Improved Data on Health Care Utilization in CS

There is a need for improved data on health care utilization by children with isolated CS. Data are needed on both health care utilization specifically related to CS treatment, and other, unrelated health care utilization. The levels and patterns of health care utilization for children with CS should be compared with those for children with no major birth defects or genetic disorders. Research should also identify any racial and ethnic, social, geographic, or socioeconomic disparities in utilization of services for CS.

Identification of the Critical Time Period of Exposure in CS

The identification of potential risk factors for CS has been severely hindered by our lack of understanding of the critical time period of exposure for this defect. Improved understanding of the time window for the onset of CS might allow identification of particular exposures during that time period that are associated with CS. To further our understanding of the timing of this defect and the critical period of exposure, studies could use human clinical assessment of timing of fusion, animal models, assessments of premature births, imaging (such as ultrasounds), and examination of spontaneous abortions.

Understanding the Observed Sex Differences in CS

Previous studies have consistently identified sex differences associated with involvement of various suture-types in children with CS, but further research is needed to identify possible explanations for these observed differences. Studies using animal models, clinical data, and genetic analyses were suggested to help clarify sex differences.

Identifying Factors That Improve Outcomes for Families

Surgical repair of CS can be very stressful not only for a child with CS, but also for his or her family. To improve outcomes for families, more information is needed on what factors can help families to better manage their child's care and treatment, both before and after surgery. Such factors might include: (1) adequacy of the information provided to families about treatment and prognosis, including longer-term outcomes, (2) treatment managed by a multidisciplinary craniofacial team, (3) access to social services, and (4) distance from source of specialized medical care. Research is needed to determine the effects of these factors and to identify the optimal service delivery methods for patients and their families.

Better Characterization of Ophthalmologic Complications Associated With CS

Very little is known about the frequency of ophthalmologic problems in children with CS and whether the problems are related to muscle or brain impairments or to another mechanism. Because ophthalmologic problems can affect learning, it is important that future studies attempt to clarify whether learning problems are associated with ophthalmologic problems or due to other aspects related to the CS.

Understanding Psychological Adjustment and Social Relationships Among Children With CS

There is a need to better understand psychological adjustment and social relationships among school-age children with CS, and whether these outcomes are affected by the type of treatment and care (multidisciplinary craniofacial team vs. non-team care). Follow-up studies of children with CS initially identified by population-based birth defects surveillance systems will permit better assessment of these outcomes in a manner that allows findings to be generalized to a broad population.

CONCLUSIONS

The goals of the public health research priorities identified at this meeting focus on improved delineation of the CS phenotype, better understanding of genetic and non-genetic factors involved in CS, and enhanced appreciation of short- and long-term outcomes for persons with CS and their families and the issues related to clinical care that could affect those outcomes. Meeting participants strongly recommended improved collaboration among clinical treatment centers and standardization of data collection to reach these goals.

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