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Risk for Developmental Delay in Non-Syndromic Craniosynostosis

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Risk for Developmental Delay in Non-Syndromic Craniosynostosis

by

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the requirements for the degree of
Doctor of Psychology

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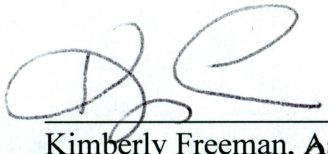
Each person whose signature appears below certifies that this doctoral project in his/her opinion is adequate, in scope and quality, as a doctoral project for the degree Doctor of Psychology.



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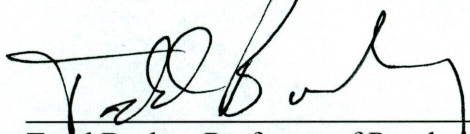

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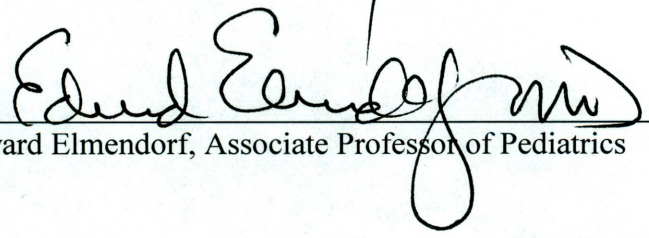

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CONTENTS

FIGURES

TABLES

ABSTRACT OF THE DOCTORAL PROJECT

Risk for Developmental Delay in Non-Syndromic Craniosynostosis

by

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Loma Linda University, September 2010
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Non-syndromic craniosynostosis is a craniofacial condition where there is a premature fusion of a calvarial suture. There are four subtypes of craniosynostosis, each one reflecting the suture that is fused (metopic, sagittal, coronal synostosis, and lambdoid synostosis). Research suggests that non-syndromic craniosynostosis is associated with an increased risk of developmental delay, behavioral problems, and learning disabilities. This was an archival study with 30 participants being treated at the Loma Linda University Children's Hospital Craniofacial Team Center. The purpose of this study was to examine the relationship between risk for developmental delay and type of craniosynostosis using the Bayley Infant Neurodevelopmental Screener. The study also investigated the relationship between risk for developmental delay and surgical treatment. Results indicated a significant relationship between subtypes of craniosynostosis and risk for developmental delay, with sagittal craniosynostosis being more likely to be at low risk for delay than metopic and coronal synostoses. There was no relationship between risk for delay and surgical treatment, likely due to a small sample size. Exploratory analyses indicated that children with craniosynostosis were more likely to be at risk for developmental delay than the general population aged 0-2 years. Future studies should focus on longitudinal designs.

Introduction

Within a few days of conception the nervous system begins to form and continues to develop throughout life. During prenatal development the nervous system is uniquely vulnerable to several risk factors that can adversely affect a child's development. It is no secret that infants born with biological (e.g., low birth weight, prematurity, medical complications) and environmental (e.g., poverty, adolescent parent, substance abuse) risk factors have a higher likelihood of developmental delay than children without these risk factors (Hess, Papas, & Black, 2004). Therefore, it is critical to be aware of risk factors and monitor children's developmental progress, especially during infancy and early childhood. If developmental delay is suspected or identified, early intervention methods can be used to treat the child and minimize or prevent future developmental problems.

Craniosynostosis, a biological risk factor, is a craniofacial condition in which one or more of the skull's sutures fuse prematurely resulting in an asymmetrical skull. It is a rare condition occurring within the population with a frequency of 1:2,000 to 1:4,000 children (Chung and Myrianthopoulos, 1975; Hunter and Rudd, 1976, 1977; Lajeunie, Le Merrer, Bonaiti-Pellie, Marchac, & Reiner, 1995, 1996; Lajeunie, Le Merrer, Marchac, & Reiner 1998; Lammer, Cordero, Wilson, Oimette, & Ferguson, 1987a, 1987b; Lima, 2004; Stephen, 2001). A normally developing newborn skull accommodates rapid growth via the presence of unfused sutures and open fontanelles or "soft spots" (Figure 1). The skull has two sets of paired sutures, the coronal and lambdoid, and two sets of single sutures, the metopic and sagittal. Some infants are born with one or more of these sutures fused creating an abnormal skull which can be the cause of intercranial pressure

and dysmorphic appearance if left untreated. Craniosynostosis has been found in syndromes such as Crouzon syndrome and Muenke syndrome among others. Isolated or single-sutured craniosynostosis refers to the premature fusion of one suture and is devoid of any other deformities. The etiology of single-suture craniosynostosis is not yet clear as studies have indicated possible genetic and several environmental causes. Furthermore, treatment for single-suture craniosynostosis entails cranioplasty usually within the first year of life in order to relieve intercranial pressure and minimize neurodevelopmental sequelae. If left untreated impaired brain growth and developmental delay is possible. Overall, findings suggest that isolated craniosynostosis is associated with a 3- to 5-fold increase in risk for cognitive deficits or learning/language disabilities (Magge, Westerveld, Pruzinsky, 2002; Shipster, Hearst, Somerville, Stackhouse, Hayward, Wade, 2003). However, other studies revealed no differences or only subtle differences in a few specific neuropsychological domains (e.g., verbal reasoning, verbal comprehension, auditory memory). Furthermore, evidence has not been established suggesting an association between fusion of a particular calvarial suture and higher risk for delay.

Despite the rationale for intercranial surgery in infants, there is as yet limited understanding of the association between single-suture craniosynostosis and neurodevelopment. Given the above, the purpose of this study is: 1) to determine the risk categories for neurodevelopmental delay of infants with metopic, sagittal, unicoronal, and lambdoid non-syndromic craniosynostosis, and 2) to determine the presence of potential benefits of surgery for infant neurodevelopment among this population.

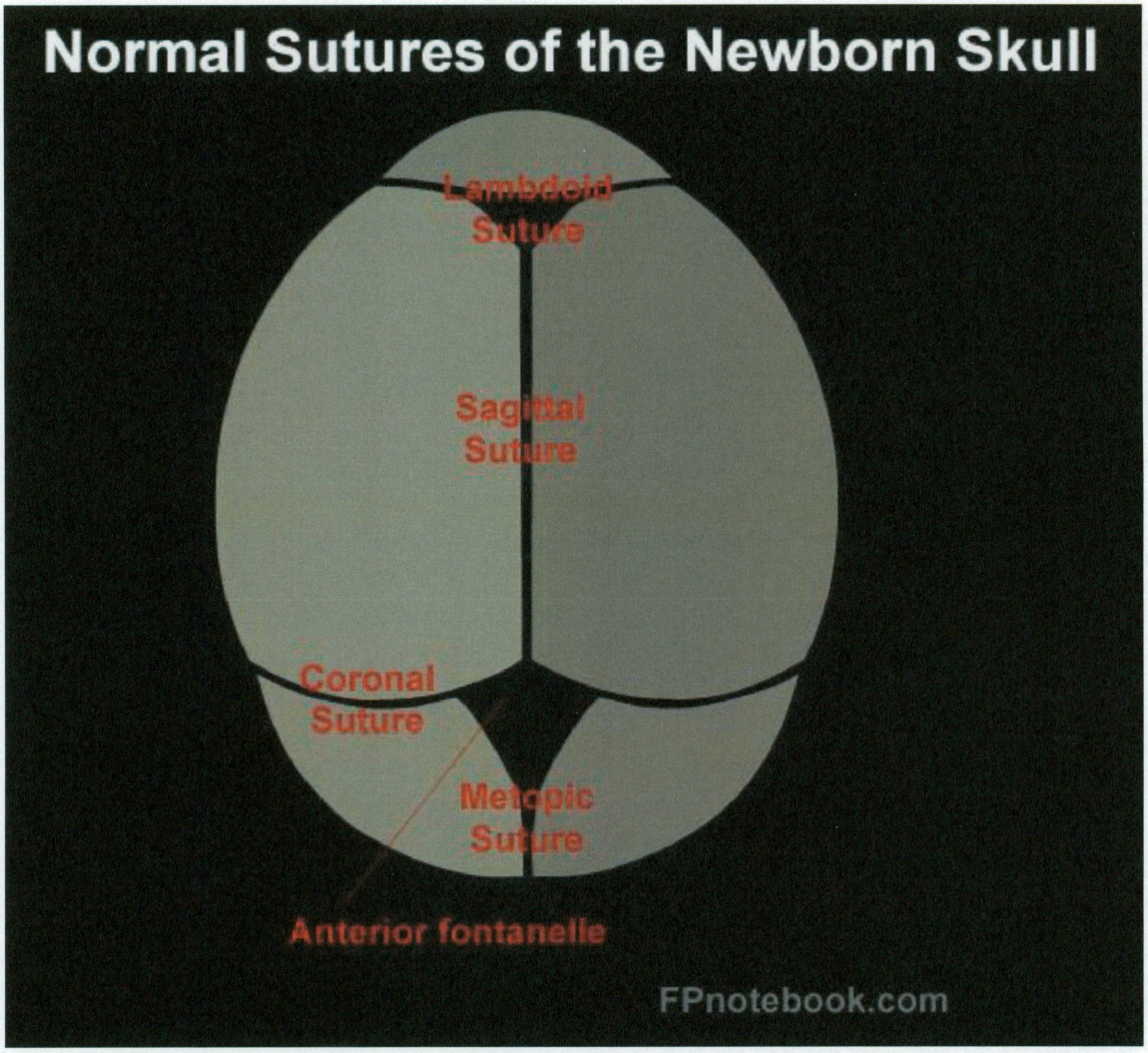

Figure 1. A normally developing skull with intact fontanelles and metopic, coronal, sagittal, and lambdoid sutures (Moses, S., 3/22/2010).

Craniosynostosis

Three different systems of discussing the craniofacial anomaly have been developed. The *morphologic system* is the classification used by practitioners interested in treatment. Individuals addressing natural history and recurrence risk focus on the etiology and use the *clinical genetic system*. Lastly, those interested in the gene pathways that impact sutural development have generated a third system called a *molecular genetic*

system. These classification systems have been developed in order to increase understanding of the problem of craniosynostosis from the perspective of different disciplines (Jones, 2002). For example, the *molecular genetic system* classifies conditions based on the specific mutation in the specific gene accounting for the developmental abnormality; while the *morphologic system* focuses on the pathology of the CNS and skull morphology and development. The focus of this study is the type and location of sutures, thus the morphologic nomenclature will be utilized.

The morphologic system of classification is based on head shape. When a baby is born, his/her brain is protected by plates of bone that are separated by sutures. There are two frontal bones, two parietal bones and an occipital bone (Figure 1). These bones are separated by sutures that meet at fontanelles. In normal development all sutures are open in a newborn and begin fusing in the first three years of life. As the baby's brain grows it pushes the plates apart and the sutures deposit bone to fill the spaces and a smooth, continuous enlargement of the skull results (Enlow, 1986). The skull has many sutures which permit growth in different directions. The sutures primarily visible from above the head are the metopic, coronal, sagittal and lambdoid sutures. The metopic suture joins the frontal bones together, while the coronal suture spans the skull from one side to the other, joining the frontal and parietal bones. The sagittal suture spans the midline of the skull, joining the two temporal bones, and the lambdoid suture spans the skull from one side to the other, joining the temporal and the occipital bones (David, Poswillo, & Simpson, 1982).

Morphologic classification. In 1851 Virchow was the first who published a *morphologic* classification system for craniosynostosis (Cohen & MacLean, 2000).

Isolated craniosynostosis is synostosis devoid of a syndrome. Syndromic craniosynostosis assumes a syndrome as part of the diagnosis. There are different types of isolated craniosynostoses which differ depending on the suture that is fused. When a suture fuses, skull growth continues in the dimensions perpendicular to the fused suture causing compensatory growth along adjacent sutures. The most common isolated craniosynostosis is sagittal synostosis, also known as scaphocephaly (Figure 2); it is the fusion of the sagittal suture, causing a long oval shaped head and has an incidence rate of 1 in 5,000 live births (Cohen & MacLean, 2000). Trigonocephaly is the fusion of the metopic suture, causing a triangular shaped head (Figure 3); it occurs at a rate of approximately 1 in 15,000 live births (Cohen & MacLean, 2000). Unicoronal synostosis (Figure 4) is when one of the coronal sutures is fused and creates an anterior plagiocephaly with restricted forward growth of the anterior cranial vault on the affected side (Kapp-Simon, Speltz, Patel, Tomita, 2007); it occurs at a rate of 1 in 11,000 live births (Cohen & MacLean, 2000). When one of the lambdoid sutures is fused (Figure 5), there is posterior plagiocephaly characterized by the flattening of the occipital bone and prominence of the mastoid bone on the involved side (Kapp-Simon, Speltz, Cunningham, Patel, Tomita, 2007); this is the least common craniosynostosis, with an incidence rate of 1 in 200,000 live births (Cohen & MacLean, 2000).

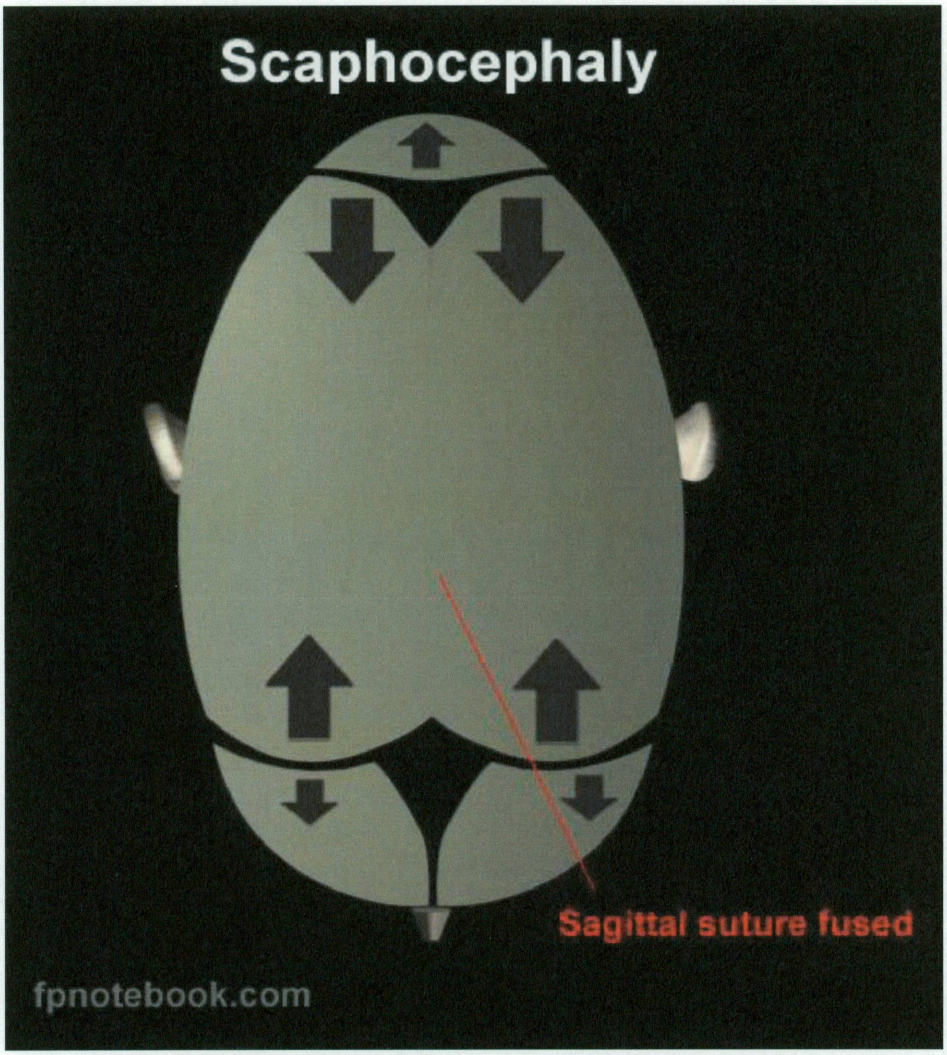

Figure 2. Scaphocephaly, the premature fusion of the sagittal suture resulting in a long oval head shape (Moses, S., 3/22/2010).

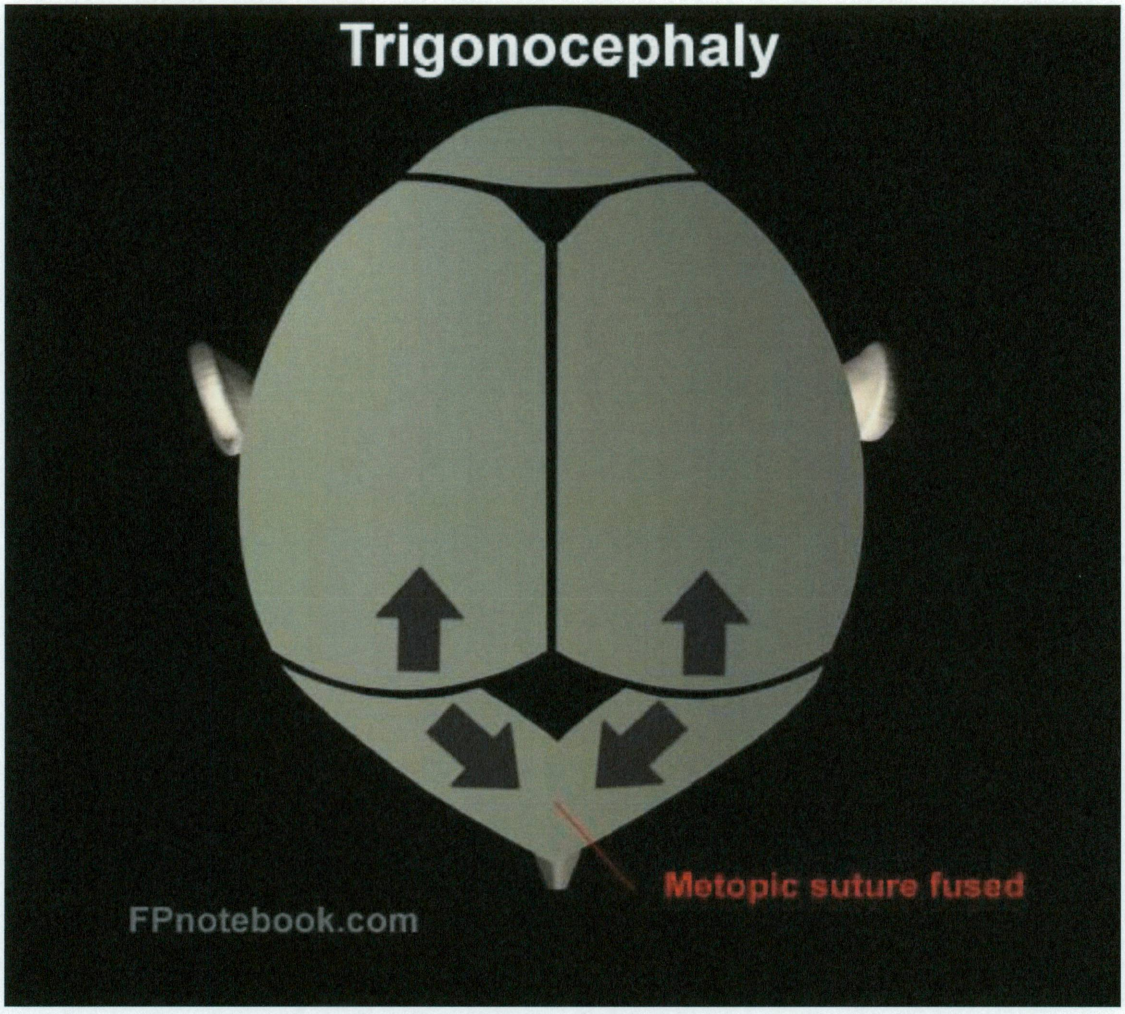

Figure 3. Triogonocephaly, the premature fusion of the metopic suture, resulting in a triangular head shape (Moses, S., 3/22/2010).

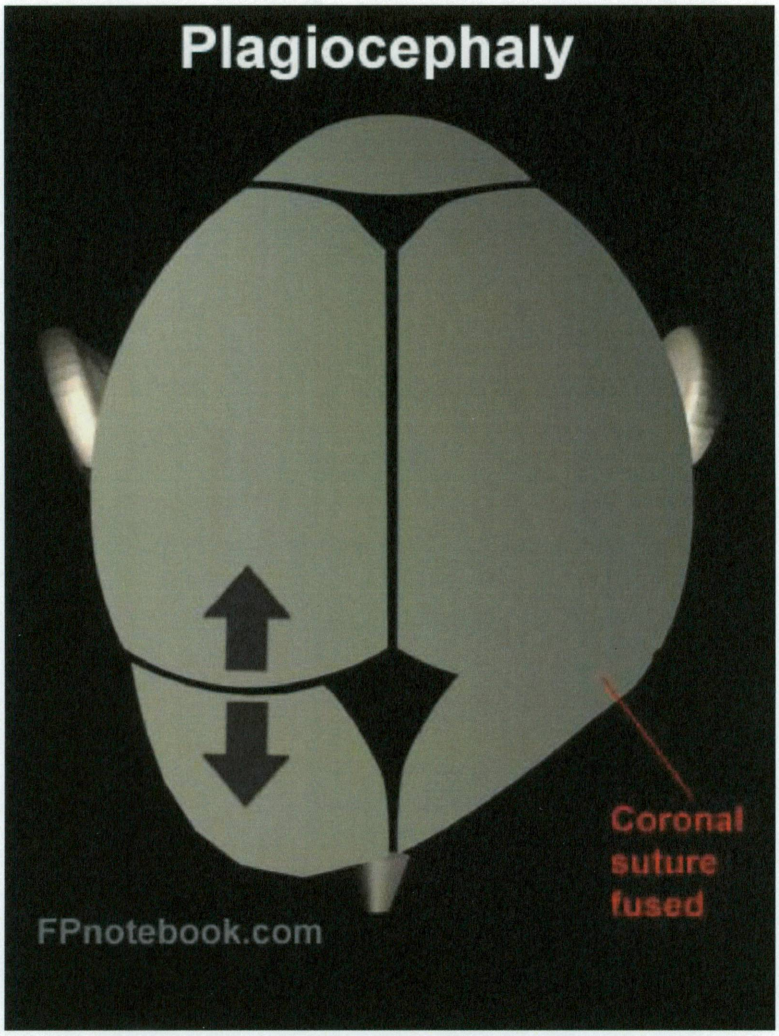

Figure 4. Unicoronal craniosynostosis, the premature fusion of one coronal suture resulting in one sided flatness of the front of the skull (Moses, S., 3/22/2010).

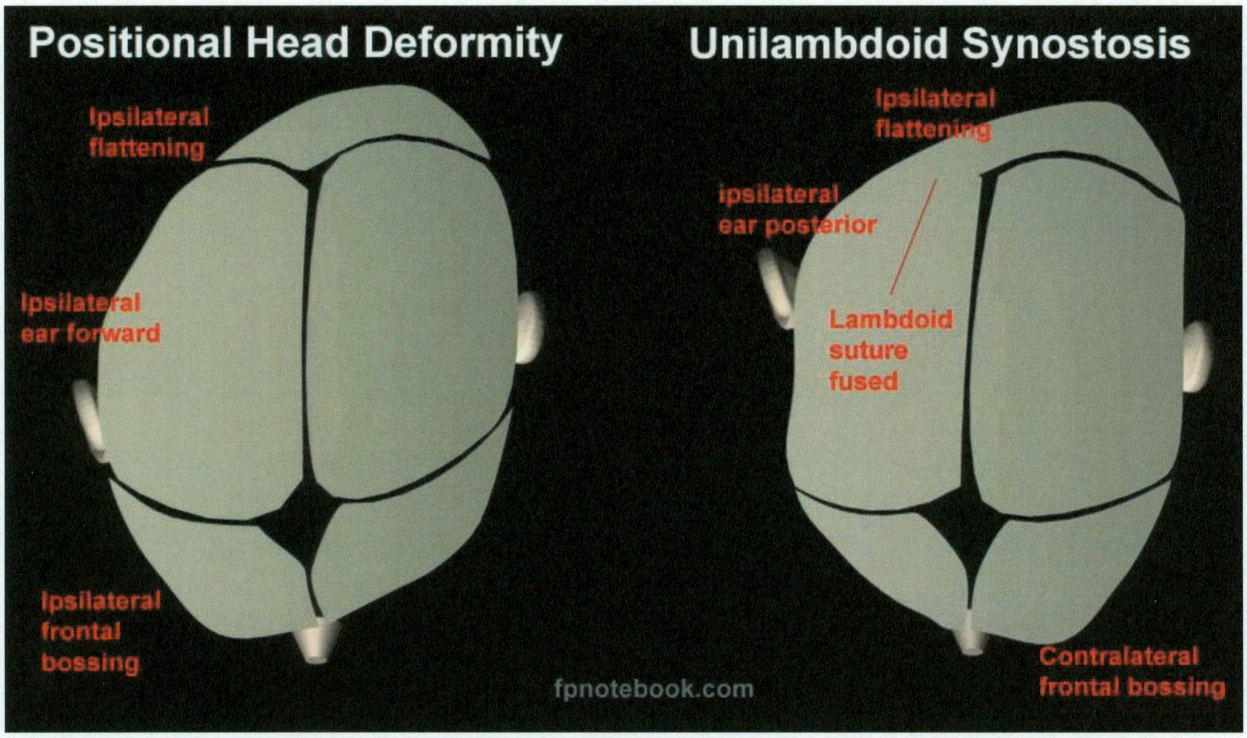

Figure 5. Positional head deformity without craniosynostosis (left); Unilambdoid craniosynostosis, the premature fusion of one lambdoid suture resulting in one sided posterior plagiocephaly (right) (Moses, S., 3/22/2010).

Syndromic craniosynostoses are less common (20%), although more than 150 syndromes have been identified. They include but are not limited to: Apert syndrome, Crouzon syndrome, Muenke syndrome, Pfeiffer syndrome, Carpenter syndrome and Saethre-Chotzen syndrome. These syndromes may have different etiologies and are expressed differently physically. They all involve craniosynostosis as well as other medical anomalies and genetic deformities (Ferreira, Collares, Ferreira, Kraemer, Filho & Filho, 2005; Jones, 2002). As this study focuses solely on non-syndromic craniosynostoses further details on syndromic craniosynostoses is not provided.

Etiologies of non-syndromic craniosynostosis. Etiology of nonsyndromic craniosynostosis has not been determined (Ferreira, Collares, Ferreira, Kraemer, Filho, &

Filho, 2006). Theories of premature suture fusion range from suspected ecological causes to evidence of familial hereditary gene mutations. Previous studies have identified potential risk factors such as: white maternal race (Alderman, Lammer, Joshua, 1988), advanced maternal age, male infant sex (Alderman et al., 1988), maternal smoking (Kallen, 1999), maternal residence at high altitudes (Alderman, Zamudio, Baron, 1995), use of nitrosatable drugs (eg, nitrofurantoin, chlordiazepoxide, chlorpheniramine) (Gardner, Guyard-Boileau, Alderman, et al., 1998), certain paternal occupations (eg, agriculture and forestry, mechanics, repairman) (Bradley, Alderman, Williams, Checkoway, Fernbach, Greene, et al., 1995), and fertility treatments (Reefhuis, Honein, & Shaw, 2003).

Familial recurrence and the discovery of rare mutations support the genetic component of craniosynostosis. There is evidence for a positive family history in approximately 6% of children with either sagittal or metopic craniosynostosis (Renier, El-Ghouzzi, Bonaventure et al., 2000). Metopic synostosis is less common than sagittal synostosis, although both conditions share similar risk factors, including 3-4 fold male predominance and an association with twinning. This suggests that sagittal and metopic craniosynostosis may have a similar pathogenesis (Say & Meyer, 1981; 2000). Both X-linked and autosomal dominant inheritance with variable penetrance have been suggested for these conditions (2000).

Unicoronal craniosynostosis is the most common hereditary form of single-suture fusion (Cunningham, Michael, Heike, and Carrie, 2007). It was first described by Glass, Champan, and Hockely (1994) when several families with hereditary nonsyndromic craniosynostosis were reported. In 1997, Muenke, Gripp, and McDonald-McGinn

reported a mutation in fibroblast growth factor receptor 3 (FGFR3^P250R) in patients with apparently isolated coronal craniosynostosis that is now known as Muenke syndrome. This FGFR3^P250R has since been identified in approximately 10% of isolated unilateral coronal synostosis and a greater percentage of bilateral cases (1997). While the FGFR3^P250R mutation is well known, other rare mutations have also been found to be associated with metopic, sagittal and coronal synostoses in children without other syndromic features (other FGFR3 mutations and TWIST1 mutations) (Cunningham et al., 2007). Cunningham and colleagues report that research suggests that mutations in genes which cause syndromic forms of craniosynostosis (Muenke, Antley-Bixler and Saethre-Chotzen syndrome) are also associated with isolated single-suture fusion without other syndromic features. Thus, they recommend that all children with isolated unilateral or bilateral coronal synostosis should be offered molecular testing for causative mutations in FGFR3 and TWIST1.

In addition, there is research investigating the etiology of premature fusions and brain dysmorphology that indicate two different perspectives. Opperman (2000) found brain dysmorphology directly associated with the suture locations, possibly indicating that brain dysmorphology can be caused by the premature fusion or skull anomaly. On the other hand, Aldridge and colleagues (2005) found dysmorphology dispersed throughout the brain not to be associated with the location of the suture. This indicates that perhaps brain dysmorphology may be the cause of premature suture fusions. In this study, Aldridge and colleagues studied the brains of infants with non-syndromic isolated right unilateral coronal synostosis (RUCS), and found many subcortical abnormalities

that were not reflected in the skull dysmorphology. This suggests that the etiology of craniosynostosis may be primarily abnormalities in the brain and secondarily in the skull.

Diagnostic methods of non-syndromic craniosynostosis. Pediatricians play a critical role in the diagnosis of craniosynostosis. Cunningham and Meike (2007) report that while most pediatric providers assess the anterior fontanelle and examine neonates for evidence of birth trauma, few providers are comfortable with normal and pathologic variation in skull shape. Craniosynostosis is usually detected in a newborn or within the first few months of life (Zumpano, Carson, Marsh, Vanderkolk, & Richtsmeier, 1999). It is common for newborns to have overriding bones of the calvarial vault for the first three days of life. However, persistent ridging at the suture lines in an abnormally shaped head is suggestive of craniosynostosis (Kabbani, & Raghuveer, 2004). Diagnosis of craniosynostosis relies on physical examination, radiographic studies including plain radiography (X-Rays) and computed tomography (CT). For single-suture non-syndromic craniosynostosis, plain radiography is sufficient (Cerovac, Neil-Dwyer, Rich, Jones, & Hayward, 2002; Goldstein and Kidd, 1982). However, CT scans have more diagnostic value because the sutures can be identified more accurately on a CT scan, and the three-dimensional product of the scan can help surgeons accurately delineate the craniofacial deformity and plan surgical reconstruction (Ghali, Sinn & Tantipasawasin, 2002).

The process of diagnosis should always include a clinical history of the patient and his/her family. Clinical history should include pregnancy complications, birth weight and duration of gestation (Panchal & Uttchin, 2003). Also, it is important to distinguish lambdoid craniosynostosis from plagiocephaly (or flattening) without synostosis, thus the history of the infant's sleeping position is necessary (Argenta, David, Wilson, & Bell,

1996). In the clinical evaluation the calvarial shape is characteristic for each type of sutural synostosis. Head circumference measurement is also critical to detect associated micro/macrocephaly.

Treatment of non-syndromic craniosynostosis. Craniosynostosis may lead to two main groups of physical problems. Raised intracranial pressure with or without hydrocephalus may be seen; although this is more common where multiple sutures are involved (Bristol, Lekovic, & Rekate, 2004; Marchac, & Renier, 1982; Renier, Brunet, & Marchac, 1987; Renier, Lajeunie, Arnaud, & Marchac, 2000). Also, deformity of both the cranial and facial skeletons may be found. To correct aesthetics or to reduce intracranial pressure, early corrective surgery may be indicated because 50% of skull growth is achieved by 6 months of age (Harrop, Avery, Marks, & Putnam, 1996; Marchac & Renier, 1987; Rannan-Eliya, Middleton, & Wall, 2002). Thus, surgical treatment remains as the primary treatment of non-syndromic craniosynostosis. The goals of surgery are to provide adequate intracranial volume to allow space for brain expansion, to minimize cognitive sequelae, and to create an aesthetically normal skull shape (Lekovik, Bristol, & Rekate, 2004). Early surgical release of the fused suture is critical to restore the normal growth pattern of the cranial vault directed by early brain development and to minimize the abnormal compensatory development of the craniofacial structures (Marsh, Jenny, Galic, Picker, and Vannier, 1991).

Developmental Implications

The skull surrounds and protects the brain providing it with space and cushion for support, thus, infant brain development is highly dependent on skull development. A

healthy brain and skull develops and grows in synchrony allowing for the appropriate space and dimensions for healthy growth (Figure 1). Thus, craniofacial anomalies have a high likelihood for brain dysmorphology and consequently risk for developmental delay. Some of the major complications associated with uncorrected craniosynostosis include increased intracranial pressure, asymmetry of the face, and malocclusion (Kabbani, & Raghuveer, 2004). Studies have demonstrated that single-suture craniosynostosis has been associated with cognitive and motor delays during infancy, both before and after surgery, and heightened risk of learning and language disabilities in school-aged children (Speltz, Kapp-Simon, Cunningham, et al., 2004). Developmental concerns potentially associated with brain functioning include mental retardation, learning disorders, and behavioral problems (Kapp-Simon, 1998). Early studies on craniosynostosis often compared infants with single-suture fusions with those of multiple suture fusions or syndromes (Anderson & Geiger, 1965; Bertelsen, 1958; Camfield & Camfield, 1986; Matson, 1968; Shillito & Matson, 1968). These descriptive studies indicated that children with single-suture fusions typically showed less impairment than those with multiple fusions, forming the impression found in many textbooks that isolated craniosynostosis had limited or no effect on brain development (Camfield & Camfield, 1986).

Results regarding developmental delay in single-suture craniosynostosis vary. Some studies suggest that children with craniosynostosis have developmental delay while others indicate no delay, and many indicate average IQ but high frequency of learning disability and speech/language problems in the school-aged populations (Magge, Westerveld, Pruinsky, and Persing , 2002; Sidoti, Marsh, Marty-Grames, and Noetzel, 1996; Virtanen, Korhonen, Fagerholm, and Viljanto, 1999).

Many studies have used the well-known Bayley Scales of Infant Development (BSID; Bayley, 1969) and Bayley Scales of Infant Development- 2nd Edition (BSID-II; Bayley, 1993), which consists of two subscales, the Psychomotor Development Index (PDI) and the Mental Development Index (MDI). There has been some consistency in this research suggesting that up to one year old infants with untreated isolated fusions have MDI scores that do not differ significantly from test norms or average control group performance (Arnaud, Reiner, & Marchac, 1995; Kapp-Simon, 1998; Kapp-Simon, Figueroa, Jocher, & Schafer, 1993; Panchal, Amirsheybani, Gurwitch, Cook, Francel, Neas, & Levine, 2001; Renier, Sainte-Rose, Marchac, & Hirsch, 1982; Speltz, Endriga, & Mouradian, 1997). However, there has been evidence for significantly lower scores of psychomotor functioning, as measured by the PDI, for infants with craniosynostosis, suggesting that motor functions may be more affected by synostosis in the first year of life than purely cognitive functions (Panchal et al., 2001). This may also be reflective of the difficulty of assessing cognitive abilities in very young children. In order to better understand the different types of craniosynostosis, more recent studies have moved beyond looking at non-syndromic craniosynostosis as a whole to examining the differences between the various subtypes. As scaphocephaly and trigonocephaly are the most common and thus the most frequently studied craniosynostoses, they will be discussed in further detail.

Developmental implications in scaphocephaly. A variety of studies focused on the school-age population, specifically on speech and language development in children with isolated sagittal synostosis. Rozelle, Marty-Frames, and Marsh conducted a study with 38 preschool and school-age children with no overt neurological deficits. Their

results indicated that out of the 38 students 29% had speech and/or language impairments (Rozelle et al., 1995). Another study supporting the notion that children with sagittal craniosynostosis may have possible language impairments was conducted by Virtanen, Korhonen, Fagerholm, and Viljanto (1999). They investigated the neurocognitive development of 18 school-age children between the ages 7 and 16 years, with isolated sagittal synostosis. Performance on assessments was compared with age- and sex-matched normally developing children. All children in the craniosynostosis group were in the Average to Low Average intelligence range. However, findings demonstrated statistically significant differences between the craniosynostosis group and the healthy controls in the auditory short-term memory subtest (Digit Span) and verbal conceptual reasoning subtests (Similarities and Comprehension) of the Wechsler Intelligence Scale for Children-Revised (WISC-R). As such, this finding suggests possible language impairment in this population.

Higher rates of learning disabilities in children with craniosynostosis who have average intelligence have been found. Magge, Westerveld, Pruinsky, and Persing (2002) studied long-term neuropsychological effects of single-suture sagittal craniosynostosis in sixteen children aged 6 to 16 who had undergone surgical treatment, with their age of surgery ranging from 35 to 316 days (mean = 117 days). The results of this study indicated significantly higher rates of learning disabilities in children with craniosynostosis than the general population. The results of intelligence testing were within the normal range, which is consistent with other studies (Kapp-Simon et al., 1993). However, results indicated a statistically significant difference between mean Verbal Intelligence Quotient (VIQ) and Performance Intelligence Quotient (PIQ) in the

study sample. Significant differences between VIQ and PIQ are suggestive of a population at higher risk for learning disabilities (Rourke, 1985). Further, half of these children were identified to have a reading and/or writing learning disability. This was higher than the prevalence rate of learning disabilities in the general population (2%-10%) (DSM-IV-TR, 2000).

Shipster, Hearst, Somerville, Stackhouse, Hayward, and Wada (2003) also studied the long-term effects of isolated sagittal craniosynostosis. They investigated the occurrence, nature, and severity of speech, language, and cognitive impairment in 76 children aged 9 months to 15 years and 7 months. Results were similar to other studies as they did not find an increased rate of global IQ deficits when compared to norms. However, results did demonstrate that a high proportion of children (28 out of 76; 37%) displayed speech and/or language impairment. This is a significantly high prevalence rate considering the 3-7% prevalence rate of speech and language impairments in normally developing school children (DSM-IV-TR, 2000). In this study, the high prevalence rate was only seen in children older than 2 years. The authors suggest that it is most likely due to the difficulty of assessing speech/language impairments in this population, as the impairments may not have become apparent yet. Often "at risk" children experience what is known as the "sleeper effect;" when their basic cognitive deficits are very subtle, they are less likely to take advantage of learning opportunities and over time these children acquire more deficits. In this study, infants were slow at learning speech and language skills which was thought to lead to more profound impairments after age 2.

Children with sagittal craniosynostosis have also been found to have neuropsychological processing deficits. Boltshauser, Ludwig, Dietrich, and Landolt

(2003) assessed 30 individuals with unoperated sagittal synostosis from age 2.5 to 25.5 (mean = 9.25 years). Seventeen siblings of the patients were used as controls. Findings indicated no differences in intelligence between the cases and siblings, and scores for both groups were higher than norms. However, despite high average intelligence, 40% of the cases evidenced neuropsychological processing deficits such as selective and sustained attention, with smaller proportions displaying deficits with processing speed and tasks assessing learning, memory, or memory span. Interestingly the siblings also displayed a high rate of deficits on selective attention and alertness. However, children with craniosynostosis differed from their siblings in their difficulties with processing speed, learning, and memory; indicating that those difficulties may be due to craniosynostosis and not familial or environmental factors.

Arnaud, Reiner and Marchac (1995) conducted a longitudinal study on children with single-suture sagittal craniosynostosis. As part of this study they selected a subset of cases assessed before 1-year of age with those assessed after 1-year of age. In the comparison of the developmental scores they found that those assessed before 1-year of age were more likely to have higher scores than those assessed after 1-year of age. They interpreted this as indicating that older infants with scaphocephaly have lower mental functioning than younger infants, most likely related to higher levels of intracranial pressure, suggesting that early cognitive development of these infants may be related to age of cranial release.

The most recently published study on craniosynostosis was conducted by Chieffo, Tamburrini, Massimi, Di Giovanni, Giansanti, Caldarelli, and Di Rocco (2010). They investigated long term outcomes of 65 adolescents who had undergone surgery for

sagittal or unicoronal craniosynostosis when they were younger than 1 year-old. The results indicated that 7 percent of adolescents with sagittal craniosynostosis demonstrated visuospatial and constructional ability defects with associated visual memory recall deficits. 17 percent also exhibited selective and sustained attention deficits. They concluded that even children who undergo early surgical treatment may still manifest lower than average results at long-term selective neuropsychological evaluations.

Developmental implications in trigonocephaly. As indicated in the above studies, children with sagittal craniosynostosis are at risk for learning disabilities and speech/language problems during school age. Research shows that children with trigonocephaly (metopic synostosis) are challenged with similar problems. Studies of mental development of children with trigonocephaly have employed different assessment methods and ages at follow-up. Consequently, there is substantial variability in the reported occurrence of developmental delays and mental retardation or impairment (Warschausky, Angobaldo, Kewman, Buchman, Muraszko, & Azengart, 2005). Depending on the study, retardation in metopic sysnostosis ranges from 0 to 20 percent (Kapp-Simon, Figueroa, Jocher, & Schafer, 1993).

Kapp-Simon, Figueroa, Jocher and Schafer (1993) conducted a longitudinal study on 25 children diagnosed with craniosynostosis. The study consisted of 7 children under the age of 3 who had an isolated metopic synostosis. Follow-up assessments were performed 7 to 13 months after corrective surgery or initial assessment if surgery was declined. The authors reported that scores ranged from borderline retardation to very superior, following a normal distribution, and that severity of anatomic craniofacial deformity and perinatal risk factors were unrelated to mental development. Furthermore,

their results indicated that after cranial release and reconstruction there were no significant changes that were positive or negative on mental development. Thus, Kapp-Simon and colleagues reported no significant delays in the metopic synostosis population.

Using a combination of chart review and parent questionnaires, Sidoti, Marsh, Marty-Grames, and Noetzel (1996) reported that 37.5% of 32 school-aged children (mean age = 8-years and 3-months) with metopic synostosis demonstrated some type of developmental problem. Eight of the patients had delayed speech and language, attention deficit/hyperactivity disorder, dyslexia, or "low IQ," while four were mentally retarded. The authors noted that identified learning and/or behavior problems increased with age and were present in both children with and without surgical correction of the synostosis. This study demonstrated that surgical correction was not indicative of a lack of developmental or behavioral problems, much like the Kapp-Simon study (1993).

Bottero, Lajeunie, Arnaud, Marchac, and Reiner (1998) also studied children with trigonocephaly. Their sample included 72 children and consisted of both isolated metopic synostosis and metopic synostosis associated with other primary defects of morphogenesis. They assessed children presurgery and postsurgery at 3 months, 1-year, and then every 2 or 3 years, assuring that the final assessment analyzed was after the age of three. Their results indicated that mental development was significantly worse when frontal synostosis was severe, when cranial reconstruction was performed after one year of age, and when there were associated extracranial malformations. Furthermore, they found no statistical difference between children aged 3 to 6 years and those who were older than 6 years (28 percent and 25 percent, respectively) with regards to developmental delay. This suggests that developmental assessments performed at 3 years

of age seem to have a good predictive value for long-term mental development (Bottero et al.). Their results also support early cranial release like the Arnaud et al. (1995) study of children with scaphocephaly.

Another study indicating language and behavioral problems in children with isolated trigonocephaly was conducted in Japan by Shimoji, Shimabukuro, Sugama and Ochiai (2002). They assessed 65 children ranging from less than 1 year-old to 9 years-old who had mild trigonocephaly and developmental delay. All their patients had symptoms such as delay in language development, hyperactivity, autistic tendencies, and motor dysfunctions. They reported that most of their patients did not display these developmental delays until after they were 1 year-old. This is congruent with other studies that have found a higher level of delay in infants that were assessed after 1 year of age, when compared to those younger than 1 year (Bottero et al., 1998; Arnaud et al., 1995). Furthermore, after decompressive craniosplasty, most of their patients (61 out of 65) improved in their clinical symptoms, especially in behavioral problems. Thus, based on these results, they postulated that mild trigonocephaly is frequently associated with developmental delays and that the symptoms can be improved to a certain degree with surgical treatment.

Kelleher, Murray, Kamel, and Earley (2006) were interested in the degree of developmental, educational, and behavioral problems in patients with nonsyndromic trigonocephaly. They also wanted to establish whether there was a lower frequency of problems in milder trigonocephaly. They reviewed 63 patient charts (15 girls and 48 boys), and contacted parents for a follow-up questionnaire including items pertaining to developmental milestones of speech and walking, assessment of the degree of help the

child needed in school, and what behavioral issues were apparent. Their results indicated a significantly high frequency of developmental, educational, and behavioral problems in non-syndromic trigonocephaly and that the frequency of these problems was not related to the severity of trigonocephaly. They also found no statistically significant difference in developmental, educational, or behavioral domains between patients who underwent surgery (70%) and those who had mild deformity and were treated conservatively (30%).

Developmental delay based on suture location. Studies of single suture craniosynostosis have not had sufficient number of participants within each diagnostic group to identify a suture-specific impact on neuropsychological processing. Only a few studies have compared development between the different subtypes of craniosynostosis. Becker, Petersen, Kane, Crandock, Pilgram, and Marsh (2005), used a retrospective chart review to examine speech, cognitive, and behavioral outcomes for 214 non-syndromic craniosynostosis patients who had documented follow-up evaluations at the average age of 6-years and 4-months. Their sample consisted of children with sagittal, metopic, right unicoronal, left unicoronal, bilateral coronal, multiple synostoses, and lambdoid synostoses. Overall, their results indicated that the affected children had higher rates of cognitive, behavioral, and speech abnormalities than that of the general population. However, the different affected sutures were similar in terms of likelihood of an abnormality. They did find that scaphocephaly was less likely to have abnormalities than patients with other affected sutures; however, this finding only approached significance ($p = 0.056$).

Kapp-Simon (1998) examined the global intellectual development and presence or absence of learning disorders in children with non-syndromic metopic, sagittal, and

unicoronal synostosis who had early surgery (under age 1), late surgery (over age 1), or no surgery across three time periods. The results provided continued evidence that during the first year of life, children with single suture craniosynostosis obtain developmental scores that do not differ from normative expectations. Results also indicated higher rates of mental retardation and learning disabilities in older children. Importantly, results also demonstrated no significant differences in mental functioning among the three diagnostic categories.

In another study by Speltz, Kapp-Simon, Collet, Keich, Gaither, Cradock, Buono, and Cunningham (2007), 125 infants with single-suture craniosynostosis (sagittal, metopic, unilateral coronal, unilateral lambdoid synostosis) and 125 case-matched healthy infants and their parents were assessed. The BSID-II was used for cognitive and psychomotor status, the Preschool Language Scale, Third Edition was used for expressive and receptive language skills, and the Wonderlic Personnel Test was used to asses maternal intelligence. Results revealed that infants with single-suture craniosynostosis had significantly lower scores on both scales of the BSID-II, than healthy infants matched for age, infant sex, family socioeconomic status, and ethnicity. Maternal IQ, infant age, gender, and location of suture did not affect the findings. Language measures revealed no group differences in expressive or receptive abilities at the age range assessed. Regarding differences of developmental status and suture location this study found no significant case-control differences; however, when comparing within groups, there were differences. Findings indicated that diagnostic subgroups varied among themselves, with the lambdoid group performing best on the MDI at a mean standard score of 95.38, metopic performing at a mean of 94.52, left coronal performing at a mean of 94.17,

sagittal performing at a mean of 90.85, and right unicoronal at a mean of 88.3. Further, the PDI scores varied from a mean of 86.6 in metopic cases to 78.0 in lambdoid cases. Sagittal cases had the highest scores on the preschool auditory comprehension measure (93.7), whereas left unicoronal cases had the highest scores on the expressive communication measure (102.7). However, participants in any of the diagnostic subgroups were not more or less likely to differ from controls. The authors stated that an adequate test of such differences will require evaluation of this cohort when a more sensitive brain-behavior relation can be assessed, such as executive functions, which could be done at an older age (Speltz et al., 2007). They also found that among both cases and controls, test scores showed some degree of correlation with age of testing. Previous investigators have been interested in the association between age of surgery and test performance in these children because of the presumption that intracranial pressure is inversely related to the neurodevelopment of the infants (Bristol, Lekovic, and Rekate, 2004; Reiner, Lajeunie, Arnaud, et al., 2000).

Developmental implications regarding surgical treatment. Another variable to consider when investigating developmental risk in children with craniosynostosis is effects of surgical treatment. Some researchers believe that surgery is primarily a cosmetic procedure (Kapp-Simon et al., 1993), while others support that cranial vault reconstruction is necessary to mitigate risk for cognitive impairment (Renier, Brunet, & Marchac, 1987). Overall, there is conflicting research regarding the hypothesis that early surgical treatment has a positive effect on global developmental functioning. Several studies found no differences in developmental status between children with craniosynostosis who underwent surgery and those who did not (Arnaud et al., 1995;

DeLeon, Speltz, & Cunningham, 2000; Kapp-Simon, 1993, 1998). These results were found regardless of location of synostosis. Some researchers demonstrated that cranial release after the child is 1-year-old resulted in lower scores on mental development (Arnaud et al., 1995; Bottero et al., 1998; Shimoji et al., 2002). On the other hand some studies did not find a difference between early surgical treatment versus late treatment (Kapp-Simon, 1998).

When children with scaphocephaly who had undergone surgery were compared to those who had not, significant differences in mental status were not found. Arnaud, Reiner and Marchac (1995) conducted a longitudinal developmental study investigating the developmental differences between children with scaphocephaly who underwent surgical treatment, and those who did not. The initial assessment was at the average age of 8 months; surgery was performed at the average age of 11 months, and follow-up assessment occurred at 6 years. There were no significant differences in mental status between operated and nonsurgically treated children at initial assessment or at 6 years of age. However, in this study as previously described, the researchers compared the mental development scores of a subset of cases who were assessed prior to one year of age and those assessed after one year of age. These children had not undergone surgical treatment, and results indicated lower mental development scores for those who were assessed later. The researchers indicated that these results may be due to higher intercranial pressure for those children over the age of one.

Another study regarding surgical treatment was conducted by Speltz, Endriga and Mouradian (1997). They studied presurgical and postsurgical mental and psychomotor development of infants with sagittal synostosis. This study included 19 non-syndromic

sagittal synostosis infants matched with 19 healthy typically developing infants. The infants were matched with respect to age, gender, ethnicity, maternal age, socioeconomic status, parity, and parent marital status. These variables were important because previous studies had not accounted for variables that have been associated with children's cognitive growth and academic performance such as family and social factors. Participants were assessed three times between 4 and 24 months with the Bayley Scales of Infant Development (BSID) in order to assess cognitive and psychomotor status. The initial assessment was presurgery and was around 4 months, and the following two assessments were postsurgery around 12 months and 24 months.

The global results of this study were consistent with previous results that cognitive and psychomotor development of infants with sagittal synostosis does not differ from normative expectations, at least in the first 2 years of life. Further, results suggested a different pattern of relations among test scores in the sagittal and comparison groups. Correlational analyses of crosstime MDI and PDI scores suggested that among infants with synostosis, presurgery developmental scores were generally less predictive of 24-month development when compared to the comparison group. In contrast, postsurgery scores of synostosis infants showed strong positive relations to 24-month performance, as did the control group scores. It should be noted that only one of these between-group comparisons was statistically significant (Time 1 and Time 3 PDI scores). The authors indicated that these findings suggest there is relatively poor presurgery to postsurgery prediction of development among infants with scaphocephaly, but good prediction afterward (1997).

Another important within-group analysis in the scaphocephaly group was the relation between MDI scores and age of surgery. Consistent with findings of Arnaud et al. (1995), there was an inverse relationship between MDI scores and age of surgery. Again, this was not statistically significant due to limited Power; however, the effect of surgery age and neurodevelopment may be clinically meaningful, especially if surgery exceeds 12 or more months like in the Arnaud et al. (1995) study. Overall, this study indicates that cognitive and psychomotor development of infants with scaphocephaly does not differ from normative expectations in the first 2 years of life, and it supports surgical treatment for scaphocephaly suggesting that treatment be completed before the age of 12 months due to an increase in the likelihood of cognitive delay after that age.

The Kapp-Simon (1998) study mentioned above also investigated the effects of surgical treatment among children with various subtypes of single-suture craniosynostosis. Overall data from this study provided little support for the hypothesis that early surgical treatment has a positive effect on global developmental functioning. However, the findings did suggest that the risk of significant delay may be greater for children with single suture craniosynostosis, regardless of surgical status than population estimates would predict. There was a retardation rate of 6.5%, which is two to three times the rate that would be expected based on normative data. While most of the children obtained scores within the normal range at each assessment, almost half of the children who were school age displayed some type of learning disorder. However, the authors note that the findings must be viewed as preliminary because of the small numbers included in the longitudinal follow-up and because formal neuropsychological assessment of the presence or absence of learning disorder was not completed. Also,

scores were compared to normative data, rather than a comparison group, making comparison less reliable.

Early Detection of Developmental Delay

"That intensive early intervention can positively alter the cognitive developmental trajectories of socially and biologically vulnerable young children; has now been demonstrated and replicated in diverse samples" (Ramey & Ramey, 1999, pp.161). There is ample evidence supporting early intervention services for children with established disabilities as well as those who are "at risk" for disabilities (Barnett, 1995; Brooks-Gunn & Hearn, 1982; Ramey, Bryant, Sparling, & Wasik, 1985; Ramey & Campbell, 1991).

Intensive early educational interventions have been documented to improve the cognitive outcomes (Barnett, 1995), and, in some cases, reduce antisocial behavior early in the school experience (Yoshikawa, 1995). Studies have revealed persistence of early-intervention effects into adolescence and young adulthood. These effects were seen in greater school achievement, (Campbell & Ramey, 1995; Campbell & Ramey, 2002), less grade retention and special education, (Campbell & Ramey, 1995; Gray, Ramey, Pungello, et al., 2002), and more high school completion (Schweinhart, Barnes, Weikart, et al., 1993) and participation in college (Campbell, Ramey, Pungello, et al., 2002). In addition to better educational outcomes, early-intervention programs have also resulted in better social outcomes such as less adolescent parenting (Campbell, Ramey, Pungello, et al., 2002), and less delinquency and fewer arrests (Schweinhart, Barnes, Wikart, et al., 1993).

Evidence for the success of early intervention has encouraged movement away from traditional models of psychological treatment delivery toward a growing interest in prevention and early intervention. In fact, various federal and state laws mandate the establishment of community-based, coordinated, multidisciplinary, family-centered programs that are accessible to children and families (Council on Children with Disabilities, 2007). Policies regarding early intervention offer services that are designed to meet the needs of children from birth to 36 months of age who have delays in one or more areas of development. These areas include physical, cognitive, communication, social, emotional, and adaptive development. Services are also available for children who have been diagnosed with a condition known to have a high probability of resulting in delayed development (2007). Further, the federal Early Periodic Screening, Diagnosis, and Treatment (EPSDT) program recommends routine developmental screening during well-child visits following a schedule determined by each state (Rosenbach & Gavin, 1998).

Since children with non-syndromic craniosynostosis have a high risk of developmental delay and school age learning disabilities, it is important to monitor their development and detect delay early in life in order to provide children and families with early intervention services such as occupational therapy, physical therapy, cognitive stimulation, speech and language therapy, behavioral health services and/or other types of interventions that will promote healthy development and most likely reduce further delay.

Children with craniofacial anomalies are usually referred to specialty craniofacial clinics where many disciplines such as plastic surgery, neurosurgery, pediatricians, dieticians, geneticists, psychologists, speech pathologists, occupational therapists, social

workers and others are involved in the child's care. At these clinics child psychologists are able to assess or screen the child's development and provide the appropriate referrals and recommendations for the families. Since the general trend in the craniosynostosis literature has suggested difficulty in detecting delay at an early age, it is imperative that a sensitive screening measure is used with this population. As mentioned above, various studies detected delay or learning disabilities in school-age children; however, limited studies have detected delay in infants and toddlers. In addressing this issue the BSID-II has shown to be somewhat promising as evidenced by the research of Speltz and colleagues (2007) previously discussed. Building on this approach, an appropriate screener that is based on the BSID-II is the Bayley Infant Neurodevelopmental Screener (BINS). This screening tool has been used for many types of at risk infant/toddler populations to predict future developmental delay in order to determine the need for early intervention. Aylward and Verhulst (2000) tested the predictability of the BINS in a longitudinal study on high-risk infants who were later assessed with the McCarthy Scales at 3 years of age. They found that the BINS was predictive of 36 month function in 18 out of 18 comparisons. Other studies have also examined the use of the BINS with children who are at high risk for developmental delays due to biological risk factors such as prematurity and low birth weight (Aylward, Verhulst, & Bell, 1996; Leonard, Piechu, & Cooper, 2001; Macias et al., 1998). Based on the good predictability value of developmental delay, the BINS appears to be an appropriate screener to use for the detection of risk for developmental delay in infants affected with non-syndromic craniosynostosis.

Statement of Problem & Hypotheses

In reviewing the literature, there are contradictory results in studies which examine the neurodevelopment of infants with non-syndromic single-suture craniosynostosis. Studies have indicated evidence supporting both normal and delayed development (Kapp-Simon, 1998; Kapp-Simon, Figueroa, Jocher, & Schafer, 1993; Panchal, Amirsheybani, Gurwitch, Cook, Francel, Neas, & Levine, 2001). Furthermore, many studies demonstrate average intelligence but a high frequency of learning disabilities, speech and language problems, and behavioral problems in school-age children with non-syndromic craniosynostosis (Magge, Westerveld, Pruinsky, and Persing , 2002; Sidoti, Marsh, Marty-Grames, and Noetzel, 1996; Virtanen, Korhonen, Fagerholm, and Viljanto, 1999). Although, there is limited research comparing developmental status of the different subtypes of craniosynostosis, some beginning trends are starting to emerge. In one of the more promising studies Becker and colleagues (2005) found that different affected sutures were similar in terms of likelihood of abnormality; however, their findings indicated a trend favoring sagittal craniosynostosis as less likely to have abnormalities. Still other studies such as Kapp-Simon and colleagues (1998) did not find differences in developmental status between the different diagnostic groups. Based on these somewhat contradictory and limited studies on neurodevelopmental outcomes in children with craniosynostosis, it is necessary to continue to study the potential differences in risk for development based on site of synostosis. This is especially true given the importance of early detection in the treatment of developmental delay (Barnett, 1995; Brooks-Gunn & Hearn, 1982). Due to its

sensitivity in assessing developmental delay, the BINS offers to be a promising and appropriate screener to utilize with the craniosynostosis population.

In addition to the above, it is also important to establish if there are benefits of surgical corrections of non-syndromic single suture craniosynostosis. Some studies indicated no significant differences in developmental status between those children who have undergone surgical treatment and those who have not had treatment (Arnaud et al., 1995; DeLeon, Speltz, & Cunningham, 2000; Kapp-Simon, 1993, 1998). Shimoji and colleagues (2002) found some improvement in language following surgery, but most of their participants remained significantly delayed. Speltz and colleagues (1997) found interesting correlational analyses of crosstime mental and psychomotor developmental scores which supports the notion that there may be benefits of surgical treatment. There are studies that found age effects indicating that surgery after age 1 resulted in lower mental development, presumably due to higher intercranial pressure (Bottero et al., 1998; Bristol, Lekovic, and Rekate, 2004; Reiner, Lajeunie, Arnaud, et al., 2000). Since there is limited and conflicting research investigating the presence of cognitive developmental benefits of surgical treatment, it would be worthwhile to investigate if surgical correction has positive developmental effects.

Given the above, the aim of this study was to examine the risk for developmental delay in infants diagnosed with single suture non-syndromic craniosynostosis. More specifically, the current study aimed to investigate potential differences in risk for delay between the different subtypes of craniosynostosis, as well as the relationship between severity of delay and surgical treatment.

Hypotheses

1) It is hypothesized that the type of craniosynostosis (metopic, sagittal, unicoronal, and lambdoid) will be related to the risk category (low, moderate, and high) for developmental delay.

2) Children with single-suture craniosynostosis who have undergone surgery will be related to the low risk category for delay on the Bayley Infant Neurodevelopmental Screener, as compared to age matched children with craniosynostosis who have not undergone surgical treatment.

Method

Participants

Archival data was used for this study; which included infants and toddlers that were part of the LLUCH Craniofacial Team Clinic (CFT), specializing in the assessment and treatment of children with craniofacial anomalies. A sample of 122 children was proposed as necessary for 80% power with a medium effect size at the 0.05 level of significance. There were 577 children that were part of the complete database obtained from the clinic. Of that sample, 35 children had nonsyndromic craniosynostosis, and of that subsample, 30 children had single-suture nonsyndromic craniosynostosis. Of the 30 nonsyndromic craniosynostosis sample, 18 had sagittal craniosynostosis, 6 had metopic, and 6 had unicoronal. Thus, 547 children were excluded from the study because they did not meet the inclusion criteria; their diagnoses included other medical conditions such as cleft lip and palate, syndromic craniosynostoses, microcephaly, and other conditions.

The inclusion criteria proposed that the participants include only those diagnosed with non-syndromic single-suture craniosynostosis; be between the ages of 3 and 24 months; and be assessed with the BINS during their regularly scheduled CFT visits. Participants identified to have other craniofacial deformities, associated syndromes, and/or medical conditions that would inherently compromise development were excluded.

Measures

Bayley Infant Neurodevelopmental Screener (BINS; Aylward, 1995). The BINS is a neurodevelopmental screener designed to assess neurological functioning and developmental status in infants between 3 and 24 months of age who have neurological problems or are at risk for developmental delay. The BINS includes subtests from the Bayley Scales of Infant Development-Second Edition (BSID-II; Bayley, 1993), as well as items measuring muscle tone and quality of movement. It is comprised of 6 item sets each appropriate for different developmental ages. The sets include 11 to 13 items and take approximately 10 minutes to administer (Aylward, 1995). Test-retest reliability is reported to range from .71 to .81 depending on the child. Internal consistency is reported to be moderate to strong. Coefficient alphas range from .73 to .85 across age. Inter-rater reliability is also established and ranges from .79-.96. Regarding construct validity of the BINS, scores have been found to be related to indices of severity of medical problems such as length of hospitalization and medical risk index for children who had been hospitalized in a neonatal intensive care unit at birth. However, the magnitude of the correlations was relatively small. Criterion validity of the BINS in a high-risk infant population was established by comparing the high-risk category with Mental Developmental Index scores < 70 on the BSID-II. Sensitivity was calculated to be 64%, and specificity 87% (Naar-King, Ellis, and Frey, p. 100, 2004). Importantly, at least two studies have been conducted examining predictive validity. The first indicated that the BINS scores at 6 months of age were significantly associated with both Mental and Psychomotor Developmental Indices of the BSID-II at 1 year of age (Macias et al., 1998). The second study suggested that children who scored in the high risk range at 6,

12, or 24 months of age had significantly lower cognitive abilities, based on intelligence tests, at 3 years of age than children in either the moderate or low risk groups (Aylward & Verhulst, 2000).

The four conceptual areas of ability assessed by the BINS are: Basic Neurological Functions/Intactness, Receptive Functions, Expressive Functions, and Cognitive Processes (NREC). Items assessing basic Neurological Functions/Intactness address the neurological integrity of the infant's central nervous system. In this domain the infant's movement, head control, and muscle tonicity are observed. Depending on the infant's age some indicators of abnormal neurological functions and risk indicators of the central nervous system include presence of drooling, motor overflow (hand mimicking or mirroring), asymmetric movement, and hypo and hypertonicity. Receptive Functions involve the entry of information into the central processing system of sensation and perception. These functions increase in complexity with development, and they include visual, auditory and tactile processing. Beginning with the development of basic and gross processing of stimuli and eventually graduating to higher-order verbal processing and distinguishing language. The Expressive Functions are the more overt behaviors that are easier to observe. The three primary areas involved are: oral motor, fine motor, and gross motor. Vocalizations such as vowel and consonant sounds and verbalizations such as word approximations or just consonant-vowel combinations are examples of oral motor items. When assessing fine motor skills manipulation of objects with fingers as well as eye-hand coordination are assessed. Gross motor skills include the development of appropriate and stable sitting, crawling and ambulating. Lastly, verbal-cognitive functions such as imitation of words and naming of objects are also assessed. The

Cognitive Processes include higher-order functioning such as, memory/language and thinking/reasoning. Goal directedness, attention, object permanence, and problem solving are also included in this category. Some examples are looking for a fallen spoon, imitation of others, building puzzles, and removing a pellet from a bottle.

The scoring for the BINS is based on Prechtl's optimality concept (1981). A measure of deviation from an established optimal neurodevelopmental status is provided and responses that are classified as optimal or desired are emphasized. The measure of deviation is based on a priori decision rules and items are scored *optimal* or *non-optimal.* For every optimal performance one point is added to the total score. Then the sum of optimal responses is compared to cut scores established by clinical and normative standardization samples, to identify the level of developmental risk. Three cut scores exist to identify infants' level or category of risk for developmental delay: Low Risk, Moderate Risk (high moderate and low moderate), and High Risk (Aylward, 1995). After scoring has been completed, the administrator begins to interpret the screener. The conceptual clusters help provide insight into whether dysfunction is global or specific.

Medical Information Form

A Medical Information Form (see Appendix A) was used to organize the necessary data extracted from the medical charts of the participants. It included the participant identification number, a number for each BINS administered, age group, gender, type of craniosynostosis, the BINS score, risk category, and type of treatment (surgery and no surgery). This form was utilized during the process of extracting and organizing participant data for the study.

Procedure

This study involved the use of archival data of infants and toddlers seen at the LLUCH Craniofacial Team Clinic, which specializes in the assessment and treatment of children diagnosed with Craniofacial Anomalies. As the study investigators were personnel in this clinic, medical records were reviewed to identify patients between the ages of 2-months, 16-days and 24-months, 15-days at the time the Bayley Infant Neurodevelopmental Screener was administered. Type of synostosis and medical treatment was also collected (see Appendix A); all data provided for this study was de-identified and anonymous.

In regards to the BINS data, at their initial visit infants through 24 months of age were routinely screened by a licensed psychologist or a trained doctoral level psychology student for developmental concerns as part of the team protocol. While the children who were at risk were screened at various intervals to monitor development, only the first screening was utilized for both analyses comparing the subtypes of craniosynostoses.

Data Screening and Analysis

Data was screened to assess for missing data and accuracy of responses. After review of all data and variables it was determined that no demographic or variable information was missing for any of the participants.

Planned Statistical Analysis

For the first hypothesis, a Chi Square Test of Independence was proposed in order to determine if there was a significant difference in the observed verses expected

frequencies in the risk categories and type of craniosynostosis. Due to a small sample size (N=30), it was necessary to combine the risk categories. Specifically, the low risk and low-moderate risk categories were combined into one risk group labeled Low Risk, and the high risk and high-moderate risk categories were combined into another group labeled High Risk. Even with this adjustment the minimum number of subjects for conducting the Chi Square was not met. Despite these limitations, the Chi Square analysis was determined to be the best statistical approach and was subsequently used.

The Chi Square statistic was also utilized for the second hypothesis, in order to determine if there was a significant relationship between children who had undergone surgical intervention and those who had not undergone surgical intervention and risk for developmental delay. As mentioned above, the sample size was too small resulting in a violation of an assumption for Chi Square; this is a limitation in the study.

Results

The final sample consisted of 30 participants, with more males (66.7%) than females (33.3%). Age groups included 3-4 months (20%), 5-6 months (13.3%), 7-10 months (26.7%), 11-15 months (20%), 16-20 months (10%), and 21-24 months (10%). Consistent with prevalence rates, majority of the participants were in the sagittal synostosis group (N=18), while the rest were evenly distributed between metopic and unicoronal synostoses (N=6 for each group). There were no children diagnosed with lambdoid craniosynostosis. Finally, there was a total of 25 participants in the non surgical treatment group (83.3%) and 5 in the post-surgical treatment group (16.7%) (see Table 1).

Hypothesis 1

It was hypothesized that the type of craniosynostosis (metopic, sagittal, unicoronal, and lambdoid) would be related to the risk category (low, moderate, and high) for developmental delay. Due to a small sample size the risk categories were combined into low risk and high risk. Additionally, the lambdoid category was not included in the analysis because there were no participants in that group. As mentioned above, a Chi Square Test of Independence was conducted resulting in a 2 x 3 contingency table. The variables were, type of craniosynostosis with three levels (sagittal, metopic, and unicoronal craniosynostoses) and risk for developmental delay (low risk, high risk).

Table 1

Demographic Characteristics of Participants (N = 30)

Characteristic	*N*	*%*
Gender		
Male	20	66.7
Female	10	33.3
Age Group		
3-4 months	6	20
5-6 months	4	13.3
7-10 months	8	26.7
11-15 months	6	20
16-20 months	3	10
21-24 months	3	10
Type of Craniosynostosis		
Metopic	6	20
Sagittal	18	60
Unicoronal	6	20
Treatment		
No surgery	25	83.3
Post-surgery	5	16.7

Statistical analysis was significant and confirmed that a difference existed between the different subgroups of craniosynostosis and risk for developmental delay, Chi Square (2, N=30) = 6.00, p = 0.05. Calculated percentages and adjusted residuals in the contingency table provided information that the observed frequency count for the sagittal group was significantly different from that which would have been expected had there been no association between the two variables in question. For example, it was

apparent that children with sagittal craniosynostosis had a significant relationship with risk category because their adjusted residuals exceeded the critical value of z = 1.96 for an alpha of .05. In addition, 90 percent of all participants in the low risk category and 45 percent of all participants in the high risk category were children with sagittal craniosynostosis. While only 10 percent of the participants in the low risk category and 25 percent in the high risk category were unicoronal participants; and 0 percent of the participants in the low risk category and 30 percent of the high risk category were metopic participants. This indicated that participants with sagittal craniosynostosis were more likely to be in low risk for developmental delay than children in the metopic and unicoronal groups.

Further descriptive statistics indicate that of the 6 participants in the metopic group, 100 percent were in the high risk category. Of the 18 participants in the sagittal group 50 percent were in the low risk category and 50 percent in the high risk category. Of the 6 participants in the unicoronal group 16.7 percent were in the low risk category and 83.3 percent in the high risk category (see Table 2).

Table 2

Percentage of Non-Syndromic Craniosynostosis in Each Risk Category (N=30)

Characteristic	*% Low Risk (N)*	*% High Risk (N)*
Type of Craniosynostosis		
Metopic	0 (0)	100 (6)
Sagittal	50 (9)	50 (9)
Coronal	16.7 (1)	83.3 (5)

Hypothesis 2

Children with single-suture craniosynostosis who have undergone surgery will be related to the low risk category for delay on the Bayley Infant Neurodevelopmental Screener, as compared to age matched children with craniosynostosis who have not undergone surgical treatment. Due to a small sample size, it was not possible to address this hypothesis as it was stated because there were 25 children that did not have surgery and 5 that had surgery. Therefore, it was not possible to match the cases by age as planned. Nevertheless, a Chi Square Test of Independence was conducted resulting in a 2 x 2 contingency table. The variables were type of treatment with two levels (surgery and no surgery) and risk for developmental delay (low risk, high risk). The results were insignificant for a relationship between type of treatment and risk for delay, Chi Square (1, N = 30) = .120, p = .729 (see Table 3).

Table 3

Percentage of No Surgery and Post-surgery Participants in Each Risk Category

Characteristic	*% Low Risk (N)*	*% High Risk (N)*
No Surgery	32 (8)	68 (17)
Post-Surgery	40 (2)	60 (3)

Descriptive statistics and frequencies were run to demonstrate the number of days between the time of surgery and the time of assessment for each child that underwent surgery (see Figure 6). The mean number of days that an assessment took place after surgery was Mean = 179.60 days.

Descriptive statistics and crosstabs were run to demonstrate the frequency of children within each craniosynostosis group that were in each risk category with and without surgery (see Table 4). The sagittal craniosynostosis group included 15 participants in the no surgical treatment group and 3 in the post-surgical treatment. Of the no surgery sagittal group N=15, 53.3 percent (8 participants), were in the low risk category and 46.7 percent (7 participants), were in the high risk category. Of the post-surgery sagittal group N = 3, 33.3 percent, 1 participant was in the low risk category and 66.7 percent, 2 participants were in the high risk category. The unicoronal craniosynostosis group included 4 participants in the no surgical group, and 100 percent were in the high risk category; while 2 participants were in the post-surgical group with 50 percent (1 participant) in the high risk and 50 percent (1 participant) in the low risk category. Lastly, the metopic craniosynostosis group included 100 percent (6 participants) in the no surgery high risk group.

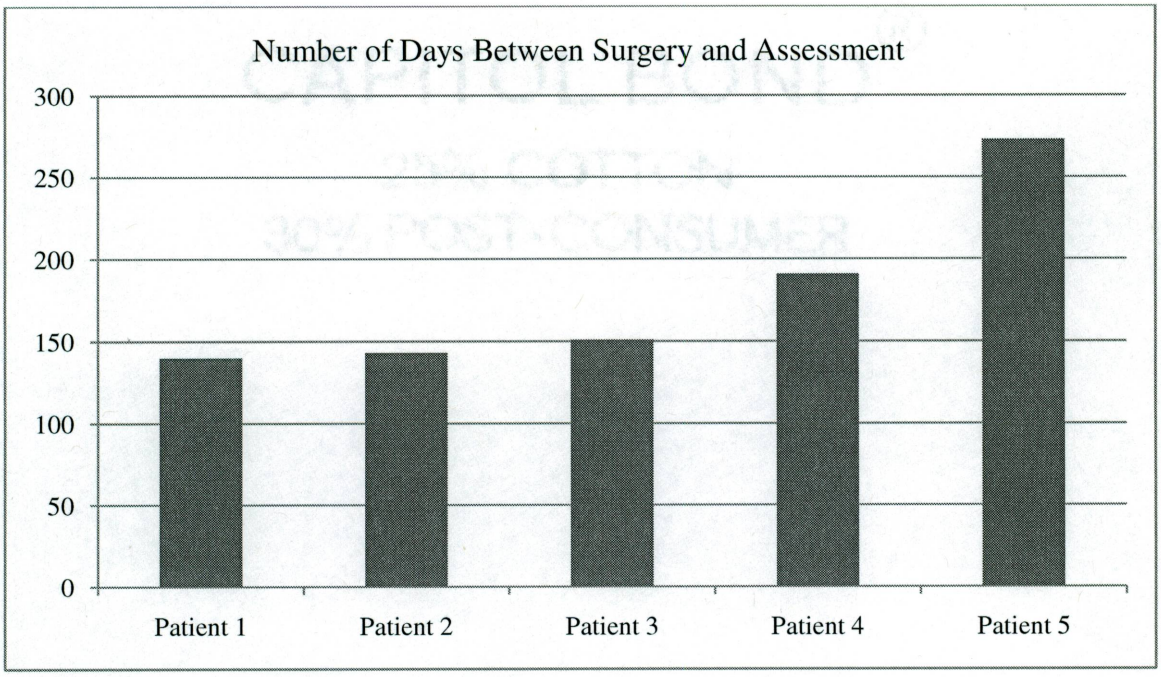

Figure 6. Duration Between Time of Surgery and Time of Assessment (N=5)

Table 4

Percentage of No surgery and Post-surgery Participants in Each Diagnostic Group

Characteristic	*% Low Risk (N)*	*% High Risk (N)*
Sagittal		
No surgery	53.3 (8)	46.7 (7)
Post-surgery	33.3 (1)	66.7 (2)
Unicoronal		
No surgery	0	100 (4)
Post-surgery	50 (1)	50 (1)
Metopic		
No surgery	0	100 (6)
Post-surgery	0	0

Exploratory Analysis

Early detection of developmental delay among children with non-syndromic single suture craniosynostosis has been inconclusive with some studies demonstrating normal development in the first year of life while other studies demonstrate developmental delay. As such, an additional analysis was conducted as an exploratory investigation to determine if this sample of children with craniosynostosis was more likely to be at higher risk for developmental delay than the general population. According to several researchers, the national prevalence rate for developmental delay in the infant/toddler population in the U.S. ranges from 3.2 percent to 23.4 percent (Blanchard, Gurka, & Blackman, 2006; Nolin, Montaquila, Nicchitta, Hagedorn, & Champan, 2004; Simpson, Colpe, Greenspan, 2003; Stevens, 2006; and Zill, & Schoenbord, 1990). This analysis aimed to examine if the prevalence rate of risk for developmental delay in the craniosynostosis population was comparable to the prevalence rate of developmental delay in the general population aged 0-2 years.

To investigate this exploratory analysis a Chi Square Goodness of Fit Test was conducted based on the low and high estimated range of the national prevalence rates of developmental delay in children age 0 to 2. According to the prevalence rate of 3.2 percent for developmental delay in the general infant/toddler population and the given sample size for the craniosynostosis group of N = 30, it was determined that the expected rate of children with craniosynostosis in the low risk for delay should be 29 and the expected rate of children in the high risk should be 1. However, the observed frequency of children in these two categories was significantly discrepant, Chi Square (1, N=30) =

390.110, p = .000, with the low risk category having 10 children and the high risk category having 20 children (see Table 4).

According to the prevalence rate of 23.4 percent and the given sample size of N = 30, it was determined that the expected rate of children with craniosynostosis in the low risk for delay should be 23 and the expected rate of children in the high risk should be 7. However, the observed frequency of children in these two categories was significantly discrepant, Chi Square (1, N=30) = 31.332, p = .000, with the low risk category having 10 children and the high risk category having 20 children. Therefore, even when analyzing this data liberally by using the low and high ranges of prevalence rates, the individuals with non-syndromic craniosynostosis are at increased risk for developmental delay than the general population (see Table 5).

Table 5

Observed and Expected Frequencies in Low and High Risk Categories Based on the Prevalence Rate of Developmental Delay in the General Population Ages 0-2 years

Category of Risk	*Observed N*	*Expected N*
3.2 % Prevalence Rate		
Low	10	29
High	20	1
23.4 % Prevalence Rate		
Low	10	23
High	20	7

Discussion

Nonsyndromic craniosynostosis has been considered by some as strictly craniofacial anomalies devoid of functional morbidity primarily due to two published reports in the 1960's indicating no signs or symptoms of functional neurologic impairment (Anderson & Geiger, 1965; Shillito & Matson, 1968). These studies were limited by a focus on mental retardation, which Kapp-Simon and colleagues noted was poorly defined (1993). Although some disagreement still exists, a growing body of more recent literature suggests that brain function may be affected by non-syndromic synostosis (Bottero, et al., 1998; Kapp-Simon et al., 2007; Speltz et al., 2004). Specifically, deficits in cognitive, behavioral, speech and/or language skills have been indicated. Further, studies are now starting to examine the difference between the subtypes of craniosynostosis and developmental implications regarding different fused sutures along with the potential treatment benefits such as surgical intervention. Because there is substantial evidence for late manifestation of developmental delay in children with craniosynostosis, it becomes important to assess and monitor this population with a sensitive and reliable measure beginning from infancy through adolescence. Early detection of delay is imperative due to the need for early intervention services when a delay exists. This study sought to examine the risk categories for neurodevelopmental delay of infants with metopic, sagittal, unicoronal, and lambdoid non-syndromic craniosynostosis, and to determine the presence of potential benefits of surgery for infant neurodevelopment among this population.

In addressing the above, the first hypothesis stated that type of craniosynostosis (metopic, sagittal, unicoronal, and lambdoid) would be related to the risk category (low, moderate, and high) for developmental delay. As proposed, results indicated a significant relationship between risk for developmental delay and type of craniosynostosis. Further investigation of the differences between the observed and expected frequencies in the Chi Square crosstabulation indicate that the sagittal craniosynostosis group is more likely to be at a lower risk for delay than the unicoronal and the metopic groups. These results support previous studies that have found children with sagittal craniosynostosis to be functioning better than other diagnostic groups (Becker et al., 2005; and Speltz et al., 2007). In their retrospective study of 214 patients, Becker and colleagues (2005) found that children with sagittal craniosynostosis were less likely to have abnormalities than patients with other affected sutures. Additionally, Speltz and colleagues (2007) found that children with sagittal craniosynostosis obtained the highest scores on the preschool auditory comprehension measure in their study. On the other hand, this same study found sagittal craniosynostosis children scored in between the other diagnostic groups on the BSID-II scales, indicating that although they did not receive the highest scores their scores still fell within the average range thus generally adding support the current findings. In contrast to the above, Kapp-Simon (1998) conducted a study resulting in no significant differences in mental functioning among metopic, sagittal, and coronal craniosynostoses. Although more studies with larger sample sizes are needed in order to substantiate these results, it is important to consider the clinical implications of this finding. Should sagittal craniosynostosis truly be at lower risk for developmental delay than the other types of craniosynostoses; then it is possible that a more rigorous early

intervention plan should be provided for those diagnosed with coronal and metopic synostosis.

One explanation for the relationship between cognitive and behavioral abnormalities and nonsyndromic craniosynostosis is that there is a primary anomaly of the brain itself, which might be specific for each type of craniosynostosis. Aldridge and colleagues used three-dimensional MRI to quantitatively compare central nervous system topographic morphologies in children with sagittal and metopic synostoses to age-matched controls (2002). The work demonstrated that neural organization of the brains of children affected with both forms of craniosynostosis differed substantially from those of children without synostosis. These differences were evident not only in cortical morphology, but in subcortical morphology as well, indicating that the developing CNS may play a role in the production of the craniosynostosis phenotype. They further stated:

> "[T]he mechanism triggering premature suture fusion may involve altered environmental conditions, anomalous genetic cascades, cell signaling mechanisms, biomechanical forces or some combination of these factors. Furthermore, the trigger may not necessarily be the same for each affected individual, depending upon the specifics of genetic background, variation in developmental timing of specific events, environment and biomechanical influences." (p. 37)

Given that the CNS is intimately involved in skull and brain development, and that there is evidence for dispersed brain dysmorphology for non-syndromic single suture craniosynostosis, it is possible that cognitive development can be affected differently and with varied severity for each child. More specifically, that each type of craniosynostosis may have different cognitive sequelae as they each have a different phenotype.

The second hypothesis also entailed a Chi Square analysis in order to determine if there was a relationship between risk for developmental delay and type of treatment. Results indicated no significant relationship; however several methodological concerns limited the validity of this result. Specifically, there was inequality of participants in the groups with 25 participants without surgical treatment and only 5 with surgical treatment. In exploring possible reasons for this discrepancy, it was noted that at the time of data collection, several of the children were within 6 months of age and had been recently diagnosed. Therefore, they did not yet have their surgeries completed. Another methodological limitation was the inability to match subjects by age or even better to assess the same children pre- and post-surgery along with a no surgery control group. In examining the results of the current study descriptively, no specific trends between the risk categories and surgery were observed. Despite these results, surgical outcome remains an important variable to investigate, as results are still inconclusive and controversial. While some studies support the need for surgery, indicating that no surgery or even late surgery after the age of 1 year, will result in developmental delay (Bottero et al., 1998; Shimoji et al., 2002), other studies indicate no differences in developmental status between children with craniosynostosis who underwent surgery and those who did not (Arnaud et al., 1995; DeLeon, Speltz, & Cunningham, 2000; Kapp-Simon, 1993, 1998).

As previously mentioned, early detection of developmental delay among infants and toddlers with non-syndromic single suture craniosynostosis has been inconclusive with some studies demonstrating normal development in the first year of life while other studies demonstrate developmental delay. As such, an exploratory investigation was

conducted in order to determine if the current sample of children with craniosynostosis was more likely to be at higher risk for developmental delay than the general population. According to several researchers, the national prevalence rate for developmental delay in the infant/toddler population in the U.S. ranges from 3.2 percent to 23.4 percent (Blanchard, Gurka, & Blackman, 2006; Nolin, Montaquila, Nicchitta, Hagedorn, & Champan, 2004; Simpson, Colpe, Greenspan, 2003; Stevens, 2006; and Zill, & Schoenbord, 1990). Chi Square Goodness of Fit Analyses were conducted based on the range of low and high prevalence rates for delay in the general population. Results indicated that even with a liberal investigation by using either the low or high range of prevalence rates, the current sample of craniosynostoses had more participants in the high risk range than was expected. In other words, the present indicates that infants and toddlers with single suture craniosynostosis are more likely to have developmental delay than the general same age population.

This is an important finding as an additional piece to this study because it provides support for early detection, monitoring of development, and early intervention services and continued funding for nationwide early intervention programs for this population. There is a large body of literature supporting early intervention services for children with established disabilities as well as those who are "at risk" for disabilities (Barnett, 1995; Brooks-Gunn & Hearn, 1982; Ramey, Bryant, Sparling, & Wasik, 1985; Ramey & Campbell, 1991). Intensive early educational interventions have been documented to improve cognitive outcomes (Barnett, 1995), reduce antisocial behavior (Yoshikawa, 1995), increase school achievement, (Campbell & Ramey, 1995; Campbell & Ramey, 2002), decrease grade retention and special education, (Campbell & Ramey,

1995; Gray, Ramey, Pungello, et al., 2002), increase high school completion (Schweinhart, Barnes, Weikart, et al., 1993) and college participation (Campbell, Ramey, Pungello, et al., 2002).

In order for an infant or toddler to receive services from early intervention programs, a family needs to prove that their child is either at risk for developmental delay or has developmental delay. The BINS is one of the few psychometrically sound tests available that allows examiners to screen young infants for developmental delays. It has a high degree of sensitivity, which is desirable in a screening instrument intended to be used in a high-risk population where underreferral for intervention services is problematic. Further, longitudinal studies have been conducted supporting the predictive value of the BINS indicating that those children who score in the "high risk" range on the BINS go on to have significantly low cognitive and intelligence scores at 3 years of age (Aylward & Verhulst, 2000). Additionally, there is evidence suggesting that testing completed at 3 years of age has good predictability of long-term mental development (Bottero et al., 1998). In sum, the BINS appears to be an appropriate screening tool to use in order to detect risk for developmental delay in infants and toddlers, as it is sensitive and has good predictability for future functioning.

Study Limitations

Although the data analyzed was collected from the Loma Linda Children's Hospital Craniofacial Clinic for several years, only 30 participants satisfied the inclusion criteria. Since this study was focused on single suture non-syndromic craniosynostosis, the inclusion criteria were stringent. Several of the children who were part of the

complete database were excluded due to having a syndrome, multiple fused sutures, or other craniofacial anomalies. Further, some of the children who met the inclusion criteria either did not follow-up at our clinic, did not need further developmental screening, or were not receiving surgical treatment during the window of data collection. As a result, the sample size necessary for power of .80 was not met indicating limited power for the study.

Furthermore, the small sample size resulted in the violation of an assumption for the Chi Square analyses. The assumption that was violated stated that no more than 25% of the cells in the Chi Square contingency table can have expected frequencies less than 5. The violation of this assumption increases the probability of making a Type II error. With a larger sample size the probability of a Type II error would decrease and possibly result in a significant relationship for the second hypothesis. A third limitation of the current study is that for some of the participants a doctoral level student in training administered the assessment while being supervised by a licensed psychologist. This process may have decreased inter-rater reliability because a student is in the learning process and may not obtain the same results that a licensed psychologist may obtain from each BINS assessment.

Another limitation of this study was the assessment measure utilized. The BINS is and appropriate measure for determining risk for developmental delay; however, limited information is available through analysis of the three-tiered classification structure. Studies conducted to date on the BINS do not clarify whether children who fall in the moderate risk group are in need of comprehensive developmental assessment or not. However, BINS scoring does allow infants in the moderate risk group categorized as high

moderate or low moderate risk which may assist with referral decisions. An assessment measure such as the Bayley Scales of Infant and Toddler Development-Third Edition can provide more information such as current developmental level for cognition, language, and motor skills. A final, limitation of this study is that participant scores were not compared to matched controls. The use of matched controls has better external validity providing scores comparable to other healthy children who have undergone the same testing procedures that the study participants underwent. As such, results would be more accurately representative of infants and toddlers in the general population.

Future Direction

There is sufficient research supporting long term negative effects of craniosynostosis, as such future research should focus on longitudinal studies of infants and toddlers with non-syndromic single suture craniosynostosis. Follow-up testing in longitudinal research would provide further insight into the deficits children with craniosynostosis develop at school age. Multisite studies are also needed in order to be able to generalize the results to a nationwide general population and have significant power with large enough sample size.

The clinical implications of this study indicate that a neurodevelopmental screener for infants diagnosed with non-syndromic craniosynostosis is warranted. A developmental screener such as the BINS is quick to administer, score, and interpret; and therefore the long term advantage of performing this screener is that it is cost effective and clinically valuable for treatment recommendations. Until further research has been done supporting and confirming the low risk for developmental delay in sagittal

craniosynostosis, it is important to assess and monitor the development of infants with all subtypes of craniosynostosis. Furthermore, based on previous research, it is apparent that even after cranioplasty children should be monitored and assessed beginning at the infancy age. Infants who are at a high moderate to high risk range for developmental delay should be further evaluated with a more comprehensive measurement tool such as the BSID-III, in order to determine the infant's strengths and weaknesses, and accordingly provide the infant with the most appropriate early intervention services.

With the use of more comprehensive neurodevelopmental assessments, infants with high moderate to high risk for developmental delays can be targeted for preventative interventions with proven efficacy (Shonkoff and Meisels, 2001). Preschool and school-age children can also be provided with specific services in order to prevent or address possible learning disabilities and behavioral problems. Continued research is necessary in order to identify treatment goals specific for this population; additionally, studies measuring the effectiveness of these interventions would benefit the field in determining the most appropriate referrals and treatment methods. Continued research with this population will help determine the specific clinical and demographic predictors of neurobehavioral outcomes, which can enhance future efforts to identify and treat high-risk cases.

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Appendix A

Medical Information Form

ID #	BINS #	Craniosynostosis Type	Gender	Age	Score	Risk Category	Type of Treatment (Y/N)