RUNNING HEAD: TRIGONOCEPHALY: NEUROBEHAVIORAL OUTCOMES OF MEDICAL

Trigonocephaly: neurobehavioral outcomes of medical risk factors

Master Thesis in Clinical and Health Psychology

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Abstract

This study examined the relationship between neurobehavioral development and medical factors for preschool children diagnosed with trigonocephaly. Data were collected for a total of 20 children, 17 boys and 3 girls, all between the age of 1.5 and 3 years at time of measurement. All of the children had recently received reconstructive surgery for their trigonocephaly. Confirming findings from other studies, the results show an increase for a broad range of neurobehavioral problems in the sample. The various medical factors also showed high values (frontal stenosis) or high prevalence (presence of comorbidity, complications during pregnancy or birth). No unequivocal relationships were found between the presence of behavioral problems and the medical factors.

Keywords: trigonocephaly; metopic synostosis; neurobehavioral development; medical factors.

Trigonocephaly: neurobehavioral outcomes of medical risk factors

As young children develop, the growth of their brain pushes the four bony plates that make up their skull outward. It is necessary for the growth of the brain that the sutures that hold these four plates together remain open. Unfortunately, for about 1 child per 2.500, one of the six main cranial sutures closes prematurely, causing a condition known as craniosynostosis. This premature closing of the sutures reduces growth of the brain and leads to deforming of the skull (or cranium) perpendicular to the closed suture (Kuper, 2000). This cranial deformation occurs mainly because the brain, not being able to grow in the direction of the prematurely closed suture, exerts more pressure in the other directions. The severity of the cranial deformation differs greatly per individual. It depends on the exact type of the (multiple) craniosynostosis and the time of closure during the development of the skull (Sadove, Klasbeck, Eppley, & Javed, 1990).

Metopic synostosis, the premature closing of the metopic suture on the forehead, is a less frequently diagnosed synostosis. There are 3.3 boys with this diagnosis for every 1 girl, and it occurs in about 1 in 15.000 live births (Sidoti, Marsh, Marty-Grames, & Noetzel, 1996; Lajeunie, Merrer, Marchac, & Renier, 1998). Lighter forms are not always recognized in practice, so this prevalence statistic might be an underestimation (Lajeunie et al., 1998). Because metopic synostosis commonly leads to a triangular cranial shape, it is commonly referred to as trigonocephaly (literally meaning triangular skull). Children with trigonocephaly often have elongated foreheads that are less rounded and more pointed. A ridge of varying size forms down the center of the forehead. Also, the eyes of these children appear closer together (a condition medically known as hypotelorism) and their eyebrows may appear to be pinched. The pressure from the growing brain sometimes causes the eyes to slightly bulge out, which may result in

problems with vision. Apart from the obvious cosmetic issues associated with trigonocephaly, the eyes of children with trigonocephaly also miss the protection that a normally developed eye socket would give.

Trigonocephaly is known to present in several forms: as an isolated, non-syndromal malformation, or in combination with other malformations. In their study of 237 patients with trigonocephaly Lajeunie et al. (1998) found that the isolated, non-syndromal form (78%) occurs more often than the combination with other malformations (17%). Finally, a very small number of cases (5%) can be categorized as part of a genetic syndrome (Lajeunie et al., 1998, 2001).

Little is known about the causes of trigonocephaly. Although the frequency of twinning for monozygotic twin pairs is three times higher than in the normal population at 8% (Lajeunie et al., 1998), this not necessarily indicate a strong genetic component. One has to consider the different mechanical in-utero situation for twins that might affect the head shape of the twins for example. While the exact details go beyond the scope of this thesis, it is helpful to know that a number of competing theories exist on the exact causes of trigonocephaly (Cohen, 1986 in Speltz, Kapp-Simon, Cunningham, Marsh, & Dawson, 2004). These theories attribute the origins of trigonocephaly to, for example: constraint by the affected suture, a primary lack of cerebral expansion, the connective tissue cells between in the cranial base and suture, or a neural tube defect preventing normal brain pulsation which stimulates cranial growth (Kuper, 2000).

Apart from the mentioned external and cosmetic consequences of trigonocephaly, the condition is thought to have a number of internal consequences as well. There is evidence that suggests that trigonocephaly might lead to a decreased blood flow (hypovascularity) in the prefrontal cortex (Sen et al., 1995; David, Wilson, Watson, & Argenta, 1996, both cited in Kuper, 2000). This decreased blood flow might lead to “a lack of cerebral development in the

underlying cerebral cortex" (Martinez-Lage, Poza, & Iluch, 1996, cited in Kuper, 2000). Additionally, Sidoti et al. (1996) note the occasional presence of small frontal lobes, when children with trigonocephaly are compared with age-controlled non-trigonocephalic children.

Neurobehavioral consequences of trigonocephaly

A lack of cerebral development in the prefrontal cortex is certain to translate to neurobehavioral consequences. This is confirmed in the literature: according to Endriga and Kapp-Simon (1999, p. 3), "a significant number of children (30% to 40% in most studies) experience difficulties with internalizing and/or externalizing problems, learning disorders, and social competence". In their review of the literature Speltz et al. (2004) also note that children with a craniosynostosis are significantly more likely to suffer from neurobehavioral difficulties. It is unknown if these neurobehavioral difficulties have neurological, psychological or even iatrogenic causes (surgery is virtually always the treatment of choice at an early age).

Before looking at causality or correlation, it is wise to first clarify the exact neurobehavioral difficulties that children with trigonocephaly seem to have. Speltz et al. (2004) summarize the following in their review of multiple types of craniosynostosis: "Isolated craniosynostosis is associated with a three- to fivefold increase in risk for cognitive deficits or learning/language disabilities" (p. 651). Although Speltz et al. (2004) include trigonocephaly in their review, only six of the seventeen studies reviewed by them include patients with trigonocephaly. The low number of studies in the review by Speltz et al. (2004) reflects the low number of available studies on the neurobehavioral outcomes associated with trigonocephaly in general. A search through the literature reveals only four recent (post 1990) studies on this particular relationship (see Table 1).

Table 1

Recent studies into neurobehavioral outcomes of trigonocephaly

Author	Sidoti et al., 1996	Kapp-Simon, 1996	Bottero et al., 1998	Shimoji et al., 2002
Number of cases	32	19	76	65
Boys (%)	75	67	82	72
Girls (%)	25	33	18	28
Measures	Self compiled test	Standardized tests	Standardized tests	Standardized tests
Other records	Record review (medical)	Record review (medical and school)	Reports from parents, teachers, and clinicians	
Results	Behavioral problems Language delay Mental retardation	Learning disorder Mental retardation	Developmental problems	Motor dysfunction Language delay Hyperactivity Poor social skills Self mutilation

The four studies (Bottero, Lajeuni, Arnaud, Marchac, & Renier, 1998; Kapp-Simon, 1996; Shimoji, Shimabukuro, Sugama, & Ochiai, 2002; Sidoti et al., 1996) show us that children with trigonocephaly suffer an increased risk for mental retardation, learning disabilities, and a broad range of neurobehavioral problems. These studies show percentages of neurobehavioral problems and learning disorders that go well beyond the 5% to 10% in the general population (Sidoti et al., 1996). It is noteworthy that the mental prognosis also seems to differ between the various types of trigonocephaly. Lajeunie et al. (1998) show that the average number of children with mental retardation (IQ < 70) for isolated trigonocephaly is around 0.5%. The retardation percentage increases to 34.4% if the children have additional malformations and ends up at 62.5% for children with an identified syndrome. The neurobehavioral problems associated with trigonocephaly range from externalizing behavior such as hyperactivity, poor impulse control,

and inattentiveness to behavior that more strongly resembles the autism spectrum disorders such as indifference to others, poor communication and speech delay (Shimabukuro, Shimoji, & Sugama, 2001; Shimoji et al., 2002, Sidoti et al., 1996; Kuper, 2000).

Externalizing problems. Some authors classify the externalizing problems associated with trigonocephaly as subtypes of ADHD (Kuper, 2000; Sidoti et al., 1996). ADHD stands for Attention Deficit Hyperactivity Disorder and refers to a diagnosis from the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), which is published by the American Psychiatric Association (1994). The most notable characteristics of children with ADHD are hyperactivity, impulsivity, and inattention. Recently the DSM-IV introduced a difference in three subtypes of ADHD: predominantly inattentive, predominantly hyperactive-impulsive, and a combined type. It has been argued that the hyperactive type is more prevalent in younger children (Lahey et al., 1998). A formal diagnosis cannot be made before the age of seven (American Psychiatric Association, 1994). However, some studies show a long-term persistence of DSM diagnosable problems for 50% of hyperactive three-year-old preschool children (McGee, Partridge, Williams & Silva, 1991). ADHD is associated with behavioral, social, and academic impairment.

According to Kuper (2000): “disruption of function of the prefrontal cortex may contribute to behavioral disturbances observed in children”. There are numerous authors that connect ADHD directly to injury or dysfunction in the prefrontal cortex. For example, Mash and Wolfe (2005) conclude in their summary of neurobiological factors that children with ADHD tend to have performance deficits on neuropsychological tests associated with prefrontal lobe functions (referring to Barkley, Grodzinsky, & DuPaul, 1992). Kuper (2000) presents a similar argument: Boucagnani and Jones (1989) showed an increase in perseverative errors and

perseverative responses for children diagnosed with ADHD on the Wisconsin Card Sorting task. This test was shown to be associated with frontal lobe damage and the activation of the dorsolateral prefrontal cortex by Berman et al. (1995). Since trigonocephaly is directly connected with multiple issues in the prefrontal cortex (decreased blood flow, lack of cerebral development, small frontal lobes) a relationship between trigonocephaly and ADHD type behavioral problems can be assumed.

Autism spectrum disorder. According to Mash and Wolfe (2005) "Autism is a severe developmental disorder characterized by abnormalities in social functioning, language and communication, and unusual behavior and interests." Autism is considered part of an entire spectrum of disorders. There are many different subtypes of autism, ranging from light to severe. Increased risk of learning disorders, attention problems, and mental retardation are commonly reported for children with trigonocephaly. Some studies however, notably the Japanese ones (Shimabukuro et al., 2001; Shimoji et al., 2002; Shimoji & Tomiyama, 2004), report problems that resemble autism. After noting post-surgery improvement in some of their patients, Shimoji et al. (2002, p.223) note: "it is therefore thought that symptoms such as delay in language development, hyperactivity, *autistic tendencies*, and self-mutilation are related to frontal lobe dysfunction" (italics added). The autistic tendencies in question are head banging and self-mutilation, among others. Mash and Wolfe (2005, p. 203) confirm: "abnormalities in the frontal lobe cortex are consistently found in individuals with autism". Regarding this evidence, it makes sense to assume a relationship between autism and trigonocephaly.

Prevalence of neurobehavioral problems

Although there are strong indications of increased risks for neurobehavioral problems in children with trigonocephaly, an exact prevalence has not been established. The great diversity in

research methods and instruments (ranging from French intelligence tests to Japanese developmental quotients) used makes the recent studies into trigonocephaly hard to compare (Bottero et al., 1998; Kapp-Simon, 1996; Shimoji et al., 2002; Sidoti et al., 1996). Given the extremely low prevalence of trigonocephaly, small sample sizes are to be expected. However this situation does increase the importance of doing studies that utilize reliable, standardized tests so that outcomes can be compared easily. Moreover, some of these studies use questionable methodologies to arrive at their conclusions. Sidoti et al. (1996), for example, used self-compiled parental questionnaires to arrive at a conclusion of "behavioral problems, including ADHD". Shimoji et al. (2002) seem to diagnose ADHD in their study – this diagnosis is questionable because it is notoriously difficult to diagnose ADHD in young children. First of all, even the normal behavior of young children oftentimes resembles ADHD type behavior and secondly, according to the DSM-IV criteria (American Psychiatric Association, 1994), ADHD is not fully diagnosable before seven years of age.

Medical factors

Trigonocephaly is often diagnosed soon after birth and early surgical correction (within the first two years) is usually the treatment of choice to lower the intracranial pressure, lower brain pressure on the eyes, and improve the child's appearance (Posnick et al., 1992). While this type of surgery certainly helps to improve the appearance of the child and relieves brain pressure, it is far less certain that surgery will actually prevent or reduce the risk of possible neurobehavioral consequences associated with trigonocephaly (Speltz et al., 2004).

Originally, Anderson, Gwin, and Todt (1962) proposed that trigonocephaly caused mental defects due to constriction of the frontal lobes by the skull. Subsequent studies showed that many patients with trigonocephaly do not develop any problems (see Shimoji et al., 2002 for

an overview). Collmann, Sorenson, and Krauss (1996) argue that frontal lobe restriction might not be the issue, but that mental deficiencies are result of coincidental poor cerebral development. What the majority of authors seem to agree on is that the prevalence of developmental delays in patients with trigonocephaly is too high to be explained by chance alone (Bottero et al., 1998; Kapp-Simon, 1996; Sidoti et al., 1996).

Given that children with trigonocephaly have an increased chance for neurobehavioral problems a new question presents itself. Why do some of these children develop problems and others not? Developmental differences between children with and without trigonocephaly could be related to the presence of metopic synostosis or its accompanying symptoms, but it could also be related to the surgery that the trigonocephalic children often receive. It might even be a combination of these two (Sidoti et al., 1996). One would suspect the cause of developmental differences to be unrelated to the surgery though because some authors (Shimoji et al., 2002) note a marked developmental improvement in children, whom had received surgery. In contrast, Sidoti et al. (1996) note a slightly higher prevalence of developmental, speech, and language problems in the operative group. Regardless, the control group from the study by Shimoji et al. (2002) clearly shows that the neurobehavioral problems can be present even without surgery.

The literature points out the existence of a number of possible medical risk factors for children with trigonocephaly. These medical factors can basically be divided in three categories. First of all the *primary diagnosis*, trigonocephaly, varies in severity from case to case. Regarding this severity, Bottero et al. (1998) note the possible negative influence on mental development of a more severe frontal stenosis (the ratio of interparietal to the intercoronal distance) or phenotype. This interparietal/intercoronal distance ratio is also used by Shimoji et al. (2002) to quantify the severity of cranial deformation. Another perspective on the severity of the

trigonocephaly would be to measure the outline of the skull and to compare it to existing norms for skull outline.

Secondly, trigonocephaly is associated with a number of *secondary medical conditions*. Both Bottero et al. (1998) and the review by Speltz et al. (2004) point out the influence of *co-existing anomalies in the brain.* It makes sense to pay special attention to the development of the *frontal lobes* of the brain given the restriction on that area by the skull. They also note the influence of *other physical malformations* on development. If secondary malformations exist they can sometimes be categorized as a syndrome (Lajeunie et al., 1998, 2001).

Finally, a number of *indirect medical factors* have an influence on the child. Bottero et al. (1998) pointed out the negative influence of *having the corrective surgery later* (after the first year of age). Lajeunie et al. (2001) add that IQ scores were significantly higher in patients that underwent surgery before 6 months of age. The development of birth and pregnancy also has an influence; especially complications during pregnancy and birth are of interest. Medication use during pregnancy is also interesting. In summary: although a number of medical risk factors have been suggested (Bottero et al., 1998; Sidoti et al., 1996; Tuite et al., 1996) the exact way by which these medical factors impact the neurobehavioral development is still largely unknown.

Research questions

Most likely due to the low prevalence of trigonocephaly, there are only a small number of recent studies that focus exclusively on the neurobehavioral consequences of trigonocephaly (Bottero et al., 1998; Lajeuni et al., 1998; Shimoji et al., 2002; Sidoti et al., 1996). Unfortunately, these studies are hard to compare to each other because they use a wide variety of (sometimes self-made) instruments to measure neurobehavioral development and problems. The studies also tend to take a narrow perspective: only direct medical factors are included. As a result of these

shortcomings, the exact prevalence of the neurobehavioral problems that children with trigonocephaly might develop is still very much debatable. Furthermore, although a number of medical factors are named as having an influence on the neurobehavioral development, it is still largely unknown which medical factors are important. As a result, the relationship between the various medical factors and possible neurobehavioral, developmental outcomes is still unknown.

The previous review demonstrated a strong need for additional research into the relationship between neurobehavioral consequences of trigonocephaly. This study will contribute to the existing literature by focusing on two areas of improvement: by using reliable, standardized instruments to promote inter-study comparison of data and by combining medical and psychological data collection while focusing exclusively on trigonocephaly. The aim of this current study is to explore the relationships between a number of medical factors and a number of neurobehavioral outcomes in young children with trigonocephaly. Being a part of a larger and more extensive study at the Erasmus MC, Sophia Children's Hospital in Rotterdam, this study will focus primarily on a young age group with children from 1.5 to 3 years of age.

The practical societal benefits of this study are clear. The results from this study might make it possible in the future to predict which of the children with metopic synostosis are at risk for neurobehavioral or developmental problems. This information will allow suitable early intervention and support programs to be implemented in a timely manner.

In order to explore the relationship between the medical factors and the behavioral outcomes it is first necessary to establish which factors and outcomes are relevant. The reviewed literature supplied a number of probable factors and outcomes (summarized in Table 2).

Table 2

Summary of the literature on medical risk factors and neurobehavioral outcomes

Medical risk factors
Severity of primary diagnosis: trigonocephaly
Secondary medical conditions
Indirect medical factors (pregnancy, surgery)
Neurobehavioral outcomes
General development (motor, cognition)
Development of language
Executive functioning
Clinical problems (ADHD, autism)

Three main research questions follow from this (I, II, and III).

I. What is the prevalence of the various neurobehavioral outcomes in the sample?

II. What is the prevalence of various suspected medical risk factors in the sample?

III. Which relationships exist between the suspected medical risk factors and the neurobehavioral outcomes for children with trigonocephaly aged 1.5 to 3 years?

Given the exploratory nature of this study it makes sense to postulate one central hypothesis based on a relative consensus in the literature (hypothesis 1).

H1. If the medical risk factors are more severe, there is a greater risk for neurobehavioral problems.

Method

Participants

The participants in this study were all young children, whom recently had reconstructive surgery for trigonocephaly at the Sophia Children's Hospital, Erasmus MC in Rotterdam. The children were between the age of 1.5 and 3 years at the time of measurement (end of 2005), giving a range of birthdates from start 09/2002 until end 03/2004. All of the participants had Dutch as a first language and a synostosis that was limited to purely the sutura metopica (trigonocephaly). Also, both isolated trigonocephaly and trigonocephaly with multiple congenital deformations (syndromal) were included. A letter was used to contact the parents of those children meeting the inclusion criteria. Since the Sophia Children's Hospital is the national center for treatment of craniosynostosis the entire population for the Netherlands was reached.

All parents agreed to participate in the study, which means that the sample is most likely equal or close to being equal to the complete Dutch population. Twenty children (3 girls, 17 boys) participated in the study. Though seemingly low, the number of participants is relatively high considering the very low prevalence of trigonocephaly in the general population. For five children some kind of visual impairment was found and four children had some kind of problem with hearing. For none of these children their visual/hearing condition prevented testing with the Mullen Scales of Early Learning. The treating physician-surgeon obtained verbal parental consent for the psychological testing and parents signed a consent form with regards to the data collection from patient records. Permission from the medical-ethical commission at the Erasmus MC has been obtained.

Measures

In order to address the main research questions it was necessary to measure the participating children both psychologically and medically. The psychological measurements provide insight in the development of cognition, emotion and behavior, while the medical measurements will provide information on the presence of the suggested risk factors.

Neurobehavioral outcomes. As summarized in Table 2, this study measures a variety of neurobehavioral outcomes for children with trigonocephaly: general development of motor skills and cognition, development of language, executive functioning, ADHD type of problems, and finally autism.

General development was measured using the Mullen Early Scales of Learning, Dutch translation (Mullen, 1995; Willigen, 2002). The Mullen Scales of Early Learning is a test for children from 1-68 months that assesses a wide variety of developmental aspects, including language, motor and perceptual abilities. It consists of a Gross Motor scale and four cognitive scales (Visual Perception Scale, Fine Motor Scale, Receptive Language Scale, and Expressive Language Scale). The standardized scores on the four cognitive scales can be summarized in a measure of *g*, a general cognitive score comparable to an IQ score (Mullen, 1995). Because no Dutch norm group data exists for this test yet, the American norm data will be used in this study. This is known to lead to a light underestimation of Dutch children. The five Mullen scales and the composite g score have a high internal consistency (Guilford's r = .75 to .83, r = .91 for the composite), supporting the interpretation of scales as separated psychological abilities (Guilford, 1954; Mullen, 1995, p. 56). Test-retest reliability is very high (ranges between r = .79 for fine motor and r = .71 for expressive language). The construct validity of the Mullen test scales is generally very high, compared with a large number of existent tests (Mullen, 1995, p. 62).

Although development of language is included in the Mullen Scales, the brief form of the N-CDI (Zink & Lejaegere, 2003) language list was added to the test battery to specifically assess language production and comprehension. The N-CDI (Zink & Lejaegere, 2002) is the result of a revision of the MacArthur Short Form Vocabulary Checklists (Fenson et al., 2000). The specific short version used in the current study was developed to facilitate quick screening for problems in the development of language (Zink & Lejaegere, 2003). Both the comprehension and production scale have a very high reliability. The internal consistency, measured using Cronbachs Alpha (Cronbach, 1951) was very high (word comprehension $\alpha > .98$ and word production $\alpha > .97$). The full N-CDIs has been proven to have high validity (Zink & Lejaegere, 2002). Because a very strong correlation (significant at $p < 0.01$) was demonstrated between both scales on the N-CDIs brief version and the full N-CDI validity is assumed for the brief version as well (Zink & Lejaegere, 2003).

Executive functioning consists of various processes that are responsible for guiding cognitive, emotional, and behavioral functions, particularly during problem solving activities (Gioia, Andrews Espy, and Isquith, 2003). Executive functioning has been strongly linked to the prefrontal brain areas in the past, which makes it especially interesting in the study of trigonocephaly. In this study the Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P) will be used (Gioia et al., 2003). Executive functioning is an umbrella construct, and the BRIEF-P reflects this fact. The BRIEF-P has multiple scales, namely inhibit (impulse control), shift (flexibility), emotional control, working memory, and plan/organize. The BRIEF-P can be administered to both parents and teacher. The BRIEF-P has a high reliability. More specifically, the internal consistency, measured using Cronbach's alpha (Cronbach, 1951), was very high (α coefficients ranging from .80 to .97 for both parent and

teacher samples). Parent ratings have only a modest correlation with teacher ratings in general (overall mean correlation $r = .19$). This is not unexpected: parents regularly rate their children as having greater problems on all scales than teachers (Gioia et al., 2003, p. 48). Establishing construct validity for the BRIEF-P is hard to because there are no similar, proven instruments that assess executive functioning. Gioia et al. (2003) do show high correlations with a variety of relevant tests that include executive functioning (including various clinical scales oriented towards ADHD and autism). The BRIEF-P may not be used for "diagnosis" of specific disorders.

ADHD and other behavioral problems were assessed using the Child Behavior Checklist (CBCL 1.5-5 years) for parents and its counterpart for teachers, the Teacher Report Form (C-TRF). The CBCL and C-TRF are designed to diagnose problematic behavior in children and has been successfully translated into Dutch (Aschenbach & Rescorla, 2000; Aschenbach, 2003; Verhulst, Koot, Akkerhuis, & Veerman, 1990). The CBCL 1.5-5 has the following scales for the parent: *Anxious-Depressed, Withdrawn Behavior, Sleeping problems, Somatic Complaints, Aggressive Behavior, Attention Problems and Delinquent Behavior,* and *Other problems*. The C-TRF has slightly different scales: *Anxious-Compulsive, Depressed-withdrawn, Fearfulness, Somatic Complaints, Immaturity, Attention problems, Aggressive Behavior,* and *Other problems*. The CBCL is an extremely wide used instrument and has shown both high reliability and validity in a large number of studies (Aschenbach & Rescorla, 2000; Aschenbach, 2003; Verhulst et al., 1990).

To screen for the possible presence of autism spectrum disorder, a translated checklist for autism in toddlers was used. The Modified Checklist for Autism in Toddlers (M-Chat) is an expanded version of the regular Checklist for Autism in Toddlers (CHAT) (Baron Cohen et al. 1996). It has been shown to have a high internal reliability (Cronbachs $\alpha = .85$). Sensitivity has

been established at 87% with a specificity of 99% at a cut-off score of three items or higher in an American sample (Robins, Fein, Barton, & Green, 2001).

Medical risk factors. In addition to the psychological measures, a number of medical measurements were collected. As summarized in Table 2, information was collected on the severity of the trigonocephaly, on secondary medical conditions, and a number of other, indirect medical factors.

The severity of the trigonocephaly was quantified as the severity of the frontal stenosis (severity of the skull deformation) and by looking at the outline of the skull (information available in patient records). The frontal stenosis was measured using the ratio of the interparietal and the intercoronal distance (Bottero et al., 1998; Shimoji et al., 2002, Sidoti et al., 1996). Bottero et al. (1998) describe this measurement on the 3D CT scan in the following way:

> Two measurements were made systematically from a slice cutting the cranial vault through the most anterolateral point of the lateral ventricles: interparietal distance, between the outer skull tables at the widest point of the skull, and intercoronal distance, between the outer skull tables at the level of the anterolateral corners of the lateral ventricles.

The advantage of using a ratio is that it can be easily comparable across studies: the type of 3D CT-scan and the exact scale of the scan do not matter because they are removed when calculating the ratio – making this a robust measurement.

A number of secondary medical conditions were measured. The presence of comorbidity or even a syndrome is derived from a number of sources: in-hospital patient records, a parental interview, and personal observations. The general development of the brain and the frontal lobe

are deduced from by radiographic reports that are included in the patient records. These radiographic reports also show the possible presence of anomalies in the brain.

Data on indirect medical factors and some general information were collected in a brief interview with the parents of the child and will be supplemented with information from the in-hospital patient records where necessary. This included information on the development of pregnancy, birth, visual/hearing impairment of the child, and medication use by mother (pregnancy) and child. The age at surgery was also deduced from the in-hospital patient records. All instruments and measures so far are summarized in Table 3.

Table 3

Measures used to assess the medical risk factors and neurobehavioral outcomes

Medical risk factors	Medical factors	Measures
Severity of trigonocephaly:	Severity of frontal stenosis (ratio)	Measurement on 3D CT-scan
	Outline of the skull	Patient records
Secondary conditions:	Comorbidity/syndrome	Patient records, interview
	Development of the frontal lobe / additional brain deformation	Radiographic reports
Indirect medical factors:	Age of the child at time of surgery	Patient records, interview
	Development of pregnancy	Patient records, interview
	Complications at birth	Patient records
Neurobehavioral outcomes		
Neurobehavioral development:	General development	Mullen Scales
	Development of language	N-CDI list, Mullen Scales
Clinical problems:	Executive functioning	BRIEF-P
	ADHD type of problems	CBCL 1.5-5 years
	Autism/autistic tendencies	M-Chat, CBCL

Procedure

The parents of the children that met the inclusion criteria for this study were contacted by means of a letter. This letter contained detailed information about the study and informed the parents that, should they participate, they are expected to pay a one-time visit to the Sophia Children's Hospital for psychological testing of their child. A permission/participation form was included that could be send back to the psychologist. Upon receiving the filled out participation form, the parents in question were contacted to set up an appointment for psychological testing in the hospital (Mullen). They were also mailed the tests to fill out at home (CBCL for both parents, BRIEF-P for both parents, a N-CDI list, and the M-CHAT). If their child was already in preschool, the preschool teacher was also requested to fill out two tests (Brief-P and C-TRF).

The mailed tests were collected during the actual visit of the parents with their child to the Children's Hospital. If the parents neglected to complete the mailed tests, they were given an additional opportunity to fill them out during or after their visit. General information was collected in a brief interview with the parents at the start of the session, after which the Mullen was used to test the child (breaks were taken when necessary). On average, the entire session took around 90 minutes per child. An experienced psychologist always supervised testing sessions. A written report with the test results for their child was send to all parents. This report included a description of the child's performance during the testing session, a brief description of the used tests, results for the various tests, and a summary of all results. All reports were reviewed and approved by an experienced psychologist.

Results

Neurobehavioral outcomes

Neurobehavioral development. Both the Mullen Scales of Early Learning and the N-CDI language list were used to assess general neurobehavioral development. Looking at *average* values for the whole sample, the Mullen Scales do not show any remarkable results. The average scores on the various scales are not substantially below the expected average. The gross motor scale is the most deviating: it has an average of 43, 7 points below the expected value of 50 on a *t*-score. Looking at specific children, one child can be classified as having mental retardation (with a general cognition score of 56, where 100 is the average standard score). These outcomes fit well with the earlier prediction that the Mullen might slightly underestimate Dutch children when using the American norm groups. More specifically focused on language development, the N-CDI language list reveals a similar outcome. When looking at average values for the entire sample, both receptive and expressive language scales have values close to the expected average of 50 (percentile).

Because both the N-CDI and the Mullen measure language on the components receptive and expressive language, it makes sense to have a closer look at the relationships between the outcomes on these two tests. This was done using Pearson's correlation (see Table 4). Results show a strong internal correlation within the N-CDI ($r = .72$, $p < .01$) and within the Mullen ($r = .77$, $p < .01$). Corresponding language scales also correlated significantly between tests: the N-CDI Expressive scale with the Mullen Expressive scale ($r = .66$, $p < .01$), and the N-CDI Receptive scale with the Mullen Receptive Scale ($r = 0.53$, $p < .05$).

Table 4

Pearson Correlation for the N-CDI & Mullen language scales

	N-CDI Receptive Language	N-CDI Expressive Language	Mullen Receptive Language	Mullen Expressive language
N-CDI Receptive Language	-	.72**	.53*	.57**
N-CDI Expressive Language		-	.38	.66**
Mullen Receptive Language			-	.77**
Mullen Expressive language				-

* $p < .05$, ** $p < .01$

Clinical problems. The BRIEF-P, CBCL and the M-Chat were used to assess possible clinical problems. Instead of focusing on general development, these tests identify and categorize problematic behavior in children. The BRIEF-P for instance aims to measure aspects of executive functioning. It was filled out by both mother and father, and where appropriate by the teacher (not all children attended preschool yet). Unlike the Mullen, an *elevated* t-score on a specific BRIEF-P scale indicates *clinical problems* with that particular aspect of executive functioning. The BRIEF-P contains two additional build-in scales that can be used to control for respondents that are overly negative towards the child (negativity scale) or that provide inconsistent answers (inconsistency scale). After reviewing these scales 2 respondents (teachers) were excluded from the sample for being inconsistent. The average BRIEF-P outcomes for both parents and teachers show scores well below the cut-off point for clinical problems ($t = 65$ or higher). The average "global executive functioning" score for teachers ($t = 57$) was slightly higher than the one reported by parents ($t = 47$ mother and $t = 47$ father).

The Child Behavior Checklist (CBCL and C-TRF) was used to assess behavioral problems on a clinical level. The CBCL was filled out by both mother and father, and where appropriate by the teacher. Looking at average values for the entire sample, results from the parents show average scores slightly above a *t*-score of 50. Only the scale "somatic complaints" is very slightly elevated ($t = 55$ for mothers). Teacher results ($n = 10$) show an average around 57. The cut off point for clinical problems on a CBCL scale is a *t*-score of 70 or higher. Somatic complaints were scored positive two times by the parents and attention problems once. The teacher results indicated problematic behavior on a variety of scales for four children out of the ten (anxious-compulsive and attention problems were found in the same child; see Table 5).

Table 5

CBCL scales: number of cases above the clinical cut-off score

CBCL Scale	Mother/father ($n = 19/16$)	CBCL Scale	Teacher ($n = 10$)
Anxious-Depressed		Anxious-Compulsive	1
Withdrawn Behavior		Depressed-withdrawn	1
Sleeping problems		Fearfulness	1
Somatic Complaints	2	Somatic Complaints	
Aggressive Behavior		Immaturity	1
Attention Problems and	1	Attention problems	1
Delinquent Behavior		Aggressive Behavior	

The M-Chat was used to check for potential autism. For the non-critical items on the M-Chat 16 children scored positive for at least one item. 3 Children scored positive on at least one critical item. A screen positive score was assigned when 2 critical positive items were found, or 3 positive items of any type. After applying this rule, 2 out of the 20 children were found screen-positive for autism in the sample.

Medical factors

The severity of trigonocephaly (frontal stenosis) was measured on the 3D CT-scan. For 5 children in the sample there was no 3D CT-scan available, so measurements were taken for 15 children. An average interparietal/intercoronal ratio of 1.33 was found. In contrast, Shimoji et al. (2002) found a ratio of 1.21 for normal children and a ratio of 1.25 for children with trigonocephaly. Unfortunately the outline of the skull revealed little information: the values noted in the sample were all well within the normal bandwidth: no abnormal values were noted.

Secondary medical conditions. Slightly less than half the children had comorbidity next to their diagnosed trigonocephaly. Out of this group, one of the children was diagnosed with Valproate syndrome (which increases the frequency of congenital malformations). Three children were diagnosed with additional dysmorphic characteristics or asymmetry of the body. Three children previously had surgery for cardiovascular pathology. Two of these children had multiple co-morbidities: one had cardiovascular pathology, pulmonary problems, and hernia inguinalis (abdominal hernia). Another had cardiovascular pathology, and dysmorphic characteristics. Finally, one child had an additional skull deformation (non-systolic plagiocephaly), one had an inner ear problem, and one had pulmonary problems. Surprisingly, parents reported medication use for only 5 of the children. Three children used asthma medication (Ventolin, Flexotide). One of the children was using laxatives, because of intestinal problems. Finally, one child used a creme for eczema.

The development of the brain and frontal lobe was assessed as well. Studying the radiographic reports in the patient records was supposed to reveal any anomalies in the development of the brain and skull other than the diagnosed trigonocephaly. Unfortunately, these

radiographic reports did not reveal much for this sample: only one report mentioned a minor abnormality (wide liquor spaces in the brain) next to the diagnosed trigonocephaly.

Indirect medical factors. Half the mothers in this study reported no problems during pregnancy. Out of the other half, 9 mothers did experience some kind of complication during pregnancy (blood loss, unusual sickness, slow growth of the child) and 1 reported having been hit by a ball in the stomach. Apart from folic acid (which is regularly prescribed in the Netherlands during pregnancy), 2 mothers reported using anti-convulsants (Valproate) during pregnancy to prevent epileptic seizures. One mother reported using Buscopan (abdominal discomfort and pain) and one mother reported Prednison (rheumatoid arthritis) and Thyrax (thyroid malfunction).

Out of the 20 children, 12 were born spontaneously, 3 were born with a caesarean section, 3 with a vacuum extraction, and 2 with forceps delivery. Out of these non-spontaneous births, 9 can be judged as very difficult births. The average APGAR scores after birth were 8 at first measurement (SD = 2.65) and 9.5 at the second measurement (SD = 0.83). The average age at surgery was 10 months, so most children had surgery before the age of one. The neonatal measures are summarized in Table 6.

Table 6

Neonatal information and age at surgery/testing

Measure	N	Mean	Std. Deviation
Pregnancy length (weeks)	20	39.58	1.94
Birth weight (gram)	20	3367.00	634.05
Age at Surgery (months)	20	10.16	2.89
Age at psychological testing (months)	20	30.54	4.78

Relationships

Though the sample size is small, there are two reasons why a certain amount of statistical analysis was still utilized in this study. The first reason is that study is part of a larger program, and results originating from this study might signal trends or tendencies that can be followed up. The second reason is the low prevalence of trigonocephaly. The size of the sample is very close to the size of the population, making the results more meaningful. It must be emphasized that results cannot be viewed as being representative, merely as a further exploration of the data.

Based on the previous results and presented data, it is now possible to address the central research question (III) of this study. The relationships between the various suspected medical risks factors and the neurobehavioral outcomes will be explored. The central hypothesis stated that there is a greater risk for *neurobehavioral problems* if the *medical risk factors* are more severe. Therefore, the emphasis in analysis is placed primarily on comparing the neurobehavioral tests that assess *clinical problems* to the three groups of medical risk factors, namely *severity of trigonocephaly*, *secondary conditions*, and *indirect medical factors*.

Severity of the trigonocephaly and clinical problems. The most direct medical measure to assess the severity of the trigonocephaly was the frontal stenosis ratio. In order to assess the relationship between this ratio and the various neurobehavioral tests that measure clinical problems, Pearson's correlation was utilized. Correlations were obtained between the IP/IC ratio and the BRIEF-P (*t*-scores), CBCL (*t*-scores), and M-Chat (sum score). Including mother, father and teacher results, a total number of 43 individual correlations were reviewed. In order to summarize, only those results are reported that have a reasonable correlation (r = .30 or higher), a reasonable significance (given the sample size, p = .20 or lower), and a valid sample size of ten or higher for the specific scale.

Table 7

Correlation between interparietal/intercoronal ratio and neurobehavioral outcomes

Measure	N	Pearson Correlation with IP/IC ratio	*p*
Mother Brief P Inhibit	14	.53	.05
Father Brief P Shift	12	-.56	.06
Mother Brief P Emotional Control	15	.45	.09
Mother CBCL Sleeping problems	14	-.52	.06
Father CBCL Anxious-Depressed	11	-.46	.16
Father CBCL Attention Problems and Delinquent Behavior	11	-.46	.16

As Table 7 shows, a small number of specific scales met these conditions. These results show that a more severe skull deformation is associated with more problems on inhibition (r = .53, p = .05) and emotional control (r = .45, p = .09). Unexpected, a more severe deformation was also correlated with less problems on flexibility (shift), less sleeping problems, less anxiety/depression, and less attention problems.

Secondary conditions and clinical problems. As seen before, slightly more than half the children had comorbidity next to their diagnosed trigonocephaly. Based on the primary hypothesis, a greater number of neurobehavioral problems would be expected in the children with comorbidity. In order to test this assumption, the means on the tests for clinical problems are compared between the group with comorbidity (n = 10) and the group without comorbidity (n = 10). Because independent sample t-tests yielded no significant results the difference between means is reported directly. Only the CBCL and BRIEF-P responses from the mother are utilized in light of small sample sizes that remain on the father and teacher reports after splitting the data.

Table 8

Differences between children with and without comorbidity

Measure		N	Average increase in score for children with comorbidity
CBCL (mother)*	Anxious-Depressed	9	0.98
	Withdrawn Behavior	9	-1.52
	Sleeping problems	9	0.00
	Somatic Complaints	9	2.61
	Aggressive Behavior	9	-0.72
	Attention Problems/Delinquent Behavior	9	-1.31
BRIEF-P (mother)*	Inhibit	9	-0.81
	Shift	10	2.80
	Emotional Control	10	1.60
	Working Memory	9	3.06
	Plan/Organize	10	-1.00
	Global executive functioning	9	0.56

* A higher score on the CBCL and BRIEF-P indicates more problems

As expected, the results in Table 8 show that the presence of comorbidity is associated with more somatic complaints on the CBCL. In line with the hypothesis, having comorbidity is also positively correlated with anxiety-depression on the CBCL. Opposite to the assumed direction however, comorbidity is associated with a lower score on CBCL scales withdrawn behavior, aggressive behavior, and attention problems/delinquent behavior. The BRIEF-P provides mixed results as well. Although the presence of comorbidity is associated with *more* problems on BRIEF-P scales flexibility (shift), emotional control, working memory, and total executive functioning, it is also associated with *lower* scores on plan/organize and inhibition.

Indirect medical factors and neurobehavioral development. A number of indirect medical factors were related to trigonocephaly earlier: *problems during pregnancy* (8 mothers), *problems during birth* (6 difficult births, some children with low APGAR scores), and *age at time of surgery.*

Problems during pregnancy. Nearly half the mothers in the sample reported some kind of problem during the pregnancy. An independent sample *t*-test was utilized to test the differences in the occurrence of clinical problems for children with and without a problematic pregnancy. Results showed no significant difference on clinical problems (BRIEF-P, CBCL and M-Chat) between children from mothers with problems during pregnancy and those without.

Problems during birth. Out of the 20 children in the sample, 6 could be described as having had a difficult birth. There were also a number of children with a notably low APGAR score. If the hypothesis is correct, the group of children with difficult births should have different scores on the clinical problem scales than those born without complications. This relationship was assessed in two ways: by comparing the occurrence of clinical problems for the 6 children with a difficult birth against the 14 without a difficult birth, and by directly correlating the APGAR scores to the various scales for clinical problems. No significant correlations were found between the APGAR scores and the CBCL, BRIEF-P and M-Chat. Furthermore, results showed no significant difference in clinical problems between children with and without a difficult birth.

Age at surgery. Finally, a Pearson's correlation was also obtained for the relationship between the age at surgery and the psychological tests for clinical problems. No significant relationships were found for the M-Chat and the CBCL. The BRIEF-P outcomes showed a trend towards significance: later surgery was associated with *lower* scores on BRIEF-P scales Inhibition ($r = -.43$, $p = .07$), Shift ($r = -.42$, $p = .06$), and Total ($r = -.43$, $p = .08$).

Discussion

The findings of this study confirmed earlier results on the prevalence of neurobehavioral outcomes in children with trigonocephaly. Regarding general *neurobehavioral development*, it seems that the children with trigonocephaly in the sample generally develop normally. The average scores on general cognition, language development, and executive functioning in the sample were quite similar to those of normal norm groups. One child was found to have mental retardation. In line with findings by Lajeuni et al. (1998), this child also suffered from multiple comorbities (heart problems and asymmetry of the body). Looking more specifically at the prevalence of *clinical problems*, the number of clinical diagnoses found was quite high given the sample size: 6 children scored positive on a CBCL scale and 2 children screened positive for autism. No clear pattern emerged from these CBCL scales: most diagnoses were found only once in the sample. In general, these results confirm the findings from the literature that children with isolated trigonocephaly do not differ that much in general development from normal children, but do suffer an increased risk for a broad range of behavioral problems (Bottero et al., 1998, Kapp-Simon, 1996, Shimoji et al., 2002, Sidoti et al., 1996, Wing, 1993).

The data on the various medical risk factors also fit findings from the literature: most medical factors show high prevalence or high values in the sample, as compared to expected values for normal control groups. Firstly the primary measure of skull deformation, the interparietal/intercoronal ratio, was found to be 1.33, where a ratio of 1.21 is found in healthy children. Almost half the children in the sample had comorbidity next to their diagnosed trigonocephaly: dysmorphic characteristics and additional problems with heart functioning were diagnosed multiple times. Problems with pregnancy (bleeding) were reported by 8 mothers. A difficult birth (non-spontaneous births) was reported 6 times.

The hypothesis proposed a positive relationship between medical risk factors and neurobehavioral problems: if the medical risk factors are more severe, there is a greater risk for neurobehavioral problems. Given the (non-longitudinal) design of this study, it follows that no causality can be deduced from the data. However, while this means that the causality behind it cannot be discovered, the hypothesis itself can be supported or rejected on basis of the data. More specifically: it can be supported if the medical risk factors are significantly, positively correlated with neurobehavioral problems. It can be rejected if no significant relationships are found or if negative relationships are found.

The hypothesis was studied in the analysis by comparing the three neurobehavioral tests that assess *clinical problems* (BRIEF-P, CBCL, and M-Chat), to the three groups of medical risk factors, namely *severity of trigonocephaly*, *secondary conditions*, and *indirect medical factors*. The severity of the trigonocephaly and the secondary medical conditions were most closely related to the actual medical diagnosis of trigonocephaly, as secondary medical conditions are often associated with trigonocephaly (for example: a syndrome). The indirect medical factors had a more supportive role in establishing the influence of problems during pregnancy, problems during birth, and age at time of surgery.

Unfortunately, although the sample showed high prevalence for various medical risk factors and neurobehavioral outcomes, very few significant relationships in support of the hypothesis were found in this study. After reviewing 43 individual correlations between the *primary measure of trigonocephaly* (the frontal stenosis ratio) and the tests for clinical problems, a mere 6 relations approached significance. These results showed that a more severe skull deformation is associated with more problems on inhibition and emotional control. At first glance these results can be interpreted as support for the assumed connection between

externalizing problems (ADHD) and trigonocephaly, possibly mediated through frontal lobe damage (Kuper, 2000; Sidoti et al., 1996). However, the four other relationships found in the same analysis contradicted both this line of reasoning and the central hypothesis completely: a more severe deformation was also correlated with less problems on flexibility (shift), less sleeping problems, less anxiety/depression, and notably: *less* attention problems.

For the *secondary medical conditions* in relationship to the clinical problems, a similar pattern was found. The presence of comorbidity was positively correlated with anxiety-depression on the CBCL and BRIEF-P scales flexibility (shift), emotional control, working memory, and total executive functioning. However, having a comorbidity was also correlated with lower score on CBCL scales withdrawn behavior, aggressive behavior, and attention problems, and BRIEF-P scales plan/organize, and inhibition. In other words, if we choose to "believe" these results a child whom has trigonocephaly and also suffers from another medical condition likely has more anxiety / depression and more issues with executive functioning. At the same time this child will have less problems with withdrawn or aggressive behavior, will have less attention problems, and less problems with planning actions. Like the outcomes for the frontal stenosis ratio, these results do not really convince: mainly because the various relationships contradict each other.

The *indirect medical factors* which were studied in relationship to the neurobehavioral, clinical problems revealed little new information: neither problems during pregnancy nor complications during birth were correlated with clinical problems. Contradicting expectations on basis of the hypothesis, a higher age at time of surgery was associated with *fewer* problems on BRIEF-P scales for inhibition, flexibility, and total.

In summary, on basis of the current data the central hypothesis cannot be accepted: a relationship between the medical "risk" factors and neurobehavioral outcomes was not established convincingly. There are two major issues that lead us to this conclusion. The first issue is the absence of significant results in favor of the hypothesis. Only one significant relationship was found that directly supported the hypothesis. One could argue that the restrictions for significance should be loosened given the small sample size and the low prevalence of trigonocephaly. However, in doing this the second issue presents itself: the non-significant relationships contradict the hypothesis just as often as they confirm it. Given these internally contradictory results, the hypothesis can not be definitively rejected or accepted.

There are a number of possible explanations for these results. The most straightforward is that the direct relationship between the medical factors and the neurobehavioral outcomes such as the one originally proposed simply does not exist. This would imply that relationships found in the current study are found by "chance" alone or that a third, unrecognized variable causes the presence of neurobehavioral problems. Although the neurobehavioral measures in this study were broad and well standardized, very few standardized medical measurements could obtained apart from the interparietal/intercoronal ratio. While it seems unlikely that the current results originate from chance alone, the presence of an unrecognized medical variable is not improbable, given the absence of multiple standardized medical measurements of the brain and cranium. Including a broader spectrum of medical tests in follow up research might resolve this issue.

A second explanation is that the assumed relationship between medical factors and neurobehavioral outcomes consists of many smaller components: individually different relationships in various directions. While this explanation certainly fits some of the results, notably the number of non-significant relationships, it faces the issue that many of these

relationships contradict each other. The severity of the skull deformation for example, was found to be associated with *more* issues on inhibition and emotional control and at the same time associated with *less* attention problems.

A third explanation is that the methodological constraints of this study have prevented it from finding clear, conclusive results. Some methodological issues might have contributed to these contradictory results. In fact, the most straightforward explanation for the contradictory results might very well be that they are simply inaccurate due to the small sample size. This small sample size, though unavoidable when studying trigonocephaly, severely limits the power and the value of statistical analysis. An internationally standardized longitudinal study or a meta-analysis of existing studies later on might be able to improve on this. Another notable methodological issue is the comparison to normative data, instead of a control group. This comparison weakens results because it is impossible to rule out the influence that the procedure of recruiting and testing the children might have had.

In conclusion: the results show an increase for a broad range of neurobehavioral problems in the sample. The various medical factors also showed high values (frontal stenosis) or high prevalence (presence of comorbidity, complications during pregnancy or birth). However, no unequivocal relationships were found between the presence of behavioral problems and the medical factors. Given the small sample size and the limited scope of this study this result must be viewed as a exploratory outcome and not as a definitive finding.

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