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Increase of prevalence of craniosynostosis☆

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ABSTRACT

Introduction: Craniosynostosis represents premature closure of cranial sutures. Prevalence is approximately 3.1–6.4 in 10.000 live births, which is reportedly rising. This epidemiologic study aims to provide insight into this rise through an accurate description of the prevalence, exploring regional variation and change over time.

Methods: The Dutch Association for Cleft Palate and Craniofacial Anomalies was consulted to identify patients with craniosynostosis born between 2008 and 2013. Data were verified using data provided by all hospitals that treated these patients. The following data were collected: date of birth, gender, diagnosis and postal code. Previously reported data from 1997 until 2007 were included to assess for change in prevalence over the years.

Results: Between 2008 and 2013 759 patients with craniosynostosis were born in the Netherlands. Prevalence of craniosynostosis was 7.2 per 10.000 live births. Sagittal synostosis was the most common form (44%). Poisson regression analysis showed a significant mean annual increase of prevalence of total craniosynostosis (+12.5%), sagittal (+11.7%) and metopic (+20.5%) synostosis from 1997 to 2013.

Conclusion: The prevalence of craniosynostosis is 7.2 per 10.000 live born children in the Netherlands. Prevalence of total craniosynostosis, sagittal and metopic suture synostosis has risen significantly from 1997 until 2013, without obvious cause.

1. Introduction

Craniosynostosis is defined as the premature closure of one or more cranial sutures, resulting in a characteristic distorted head shape and an increased risk of elevated intracranial pressure. The prevalence, according to the best available sources, ranges from 3.1 to 6.4 in 10.000 live births (Boulet et al., 2008, French et al., 1990, Kweldam et al., 2011, Lajeunie et al., 1995, Singer et al., 1999). In 21% it is caused by a known genetic disorder, the remaining 79% are considered non-syndromic craniosynostosis (Wilkie et al., 2010, Sharma et al., 2013).

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The commonest single-suture craniosynostosis form is sagittal suture synostosis, comprising approximately 40–60% of single-suture craniosynostosis patients (Boulet et al., 2008, Kweldam et al., 2011, Singer et al., 1999, Wilkie et al., 2010, Lee et al., 2012, Selber et al., 2008, van der Meulen et al., 2009). A rise of metopic suture synostosis has been reported, reflecting the changing demographics of craniosynostosis in both Europe and the United States (Kweldam et al., 2011, Selber et al., 2008, van der Meulen et al., 2009, Di Rocco et al., 2009).

Since 1991 the Dutch Association for Cleft Palate and Craniofacial Anomalies has kept record of all craniosynostosis patients born in the Netherlands. This continuous professional-based registry enables an accurate estimate of the prevalence of the different forms of craniosynostosis, assuming all cases are detected at some stage. Previous research at our center reported the prevalence of sagittal and metopic suture synostosis using this database and consulting the treating hospitals for the years 1997–2007 (Kweldam et al., 2011). Recently we notified a steady increase of the number of cases referred to our unit. This may reflect changing awareness of parents or caregivers, changing referral patterns, or may indeed reflect changing epidemiology. The epidemiologic study presented here aims to provide evidence on the background of this increase, through an accurate description of the prevalence of each type of non-syndromic and syndromic craniosynostosis, exploring regional variation and change over time.

2. Materials and methods

This study was approved by the institution's medical ethical board: MEC-2015-117. The approval included the use of registry data. As this was a retrospective study with an anonymous data-extract formal consent was not required.

The national registry of the Dutch Association for Cleft Palate and Craniofacial Anomalies (*Nederlandse Vereniging voor Schisis en Craniofaciale Afwijkingen)* —the Dutch national registration authority for cleft lip/palate and craniofacial anomalies — was consulted to identify patients with craniosynostosis born between 2008 and 2013. This register contains anonymous data of all craniosynostosis cases coming under professional care. A data extract was provided containing birth date, gender, diagnosis and the registering center. The data obtained through this national register were verified at the local level i.e. the individual hospitals (all tertiary centers) where the patients were treated: Sophia Children's Hospital – Erasmus Medical Center, Rotterdam; Radboud University Medical Center, Nijmegen; Maastricht University Medical Center, Maastricht; Academic Medical Center, Amsterdam; University Medical Center, Utrecht. Subsequently the postal codes of the included cases were supplied by the treating hospitals to enable epidemiological analysis.

Patients with the following diagnoses were included in the study:

- Single suture craniosynostosis: sagittal, metopic, coronal, lambdoid or fronto-sphenoidal synostosis.
- Syndromic craniosynostosis: Apert's, Crouzon-Pfeiffer's, Muenke's, and Saethre-Chotzen's syndrome, craniofrontonasal dysplasia (CFND) with craniosynostosis, Carpenter syndrome, TCF12-related craniosynostosis and all other known genetic mutations such as IL11RA, ERF and MSX2.
- Complex craniosynostosis: Multiple suture synostosis, without known genetic cause.

Data collected included: date of birth, gender, diagnosis and (crude) postal code. Four-digit postal enable analysis of geographical epidemiology including variation in detection of craniosynostosis.

Only patients with primary craniosynostosis were included, i.e. cases were excluded with secondary craniosynostosis due to, for example, a VP-shunt or microcephaly. Additional exclusion criteria were: 1) patients with a metopic ridge only, a very mild form of trigonocephaly with no indication for surgical intervention; 2) patients with craniosynostosis born abroad, but treated in the Netherlands.

The Dutch perinatal registry registers all births in The Netherlands. The birth data for the years 2008–2013 were obtained from their annual public reports (Perinatal Registry, 2012, Perinatal Registry, 2013). A Poisson regression analysis was performed to assess for an increase or decrease in prevalence of the different subtypes of craniosynostosis. The total live birth count of the Netherlands from 2008 to 2013 was included in this analysis as offset.

Subsequently data derived from an earlier paper by Kweldam et al. covering 1997–2007 were included to assess for change in prevalence of total craniosynostosis and more specifically for metopic and sagittal synostosis (Kweldam et al., 2011). For the other subtypes of craniosynostosis these data were not available in sufficient detail. For the combined dataset a Poisson regression analysis was performed.

The Netherlands is since 1960 subdivided into approximately 4000 4-digit postal codes. In the present study the 4-digit postal codes were grouped into 6 different regions, based on state boundaries and regional referral patterns (Fig. 1). To assess the regional evenness of prevalence the prevalence of craniosynostosis in these areas was related to the birth rate of these regions, provided by the Dutch Perinatal Registry, the online data of Statistics Netherlands, and reports relying on these sources (Steketee et al., 2012). The absence of regional prevalence differences was tested using a standard chi-square test.

3. Results

Between January 1st 2008 and December 31st 2013, 759 patients with craniosynostosis were born in the Netherlands. Single suture craniosynostosis occurred in 666 patients (87.7%), while syndromic and complex craniosynostosis represented 93 of the cases (12.2%) (Table 1, Fig. 2). The overall prevalence for craniosynostosis was 7.2 per 10.000 live births (about 1:1400). The male:female ratio was 2.2:1 for the whole study population, while this ratio was 2.5:1 in single suture craniosynostosis and 1:1.1 in syndromic cases.

To achieve the highest accuracy in the registered numbers of all subtypes the registry of the Dutch Association for Cleft Palate and Craniofacial Anomalies the data was cross referenced with the data provided by the treating hospitals. In total the hospitals reported 65 patients whom were not registered at the national registry.

3.1. Single suture craniosynostosis

In total, 666 patients with single suture craniosynostosis were identified. The prevalence of single suture craniosynostosis was 6.3 per 10.000 live-births. Absolute numbers and prevalence of all subtypes during the complete study period are shown in Table 1 and Fig. 3.

Male:female ratios were 3.9:1 for sagittal, 3.0:1 for metopic, 1:3.6 for unicoronal and 3:1 for unilambdoid synostosis. All frontosphenoidal synostosis patients ($n = 4$) in this study were male.

The 73 patients with unicoronal synostosis were coded as apparently non-syndromic, based on clinical evaluation. In 43 of these patients (59%) this clinical evaluation was confirmed by