ABSTRACT

Objective: To evaluate the association between prematurity (by the gestational week) and attention-deficit hyperactivity disorder (ADHD) during childhood.

Methods: Observational, matched cohorts study using data from children born in a tertiary-level hospital (Hospital Vall d'Hebron, Catalonia, Spain) during 1995-2007 and data from the Information System for Development of Research in Primary Health Care (SIDIAP database, Catalonia, Spain).

Results: Prevalence of ADHD increases as gestational age decreases: 12.7% for those born ≤28weeks of gestation (, compared to 3.2% and for those born after the 37 weeks of gestation. The risk of developing ADHD decreases as gestational weeks increase [35-36 gw HR 5.57 (2.49-12.46), 29-32 gw HR 2.37 (1.54-3.63), 33-34 gw HR 3.38 (2.08-5.50) and 35-36 gw HR 1.70 (1.19-2.44)].

Conclusions: Being born premature is associated with a risk of developing ADHD in late premature and early premature children. Attention when taking care of these infants regarding their mental health must be made.

Kew words: premature, child, Attention Deficit Disorder with Hyperactivity, Psychotropic Drugs

INTRODUCTION

Prematurity constitutes a worldwide health problem and leads to high costs in public healthcare (Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes; Behrman RE, Butler AS, 2007; R. E. Behrman and A. S. Butler (Eds), 2007). The World Health Organization (WHO) reports a percentage of 9.6% premature births (March of Dimes, PMNCH, Save the children, 2012).

Several studies and meta-analysis show that premature children have moderate to severe deficits in academic achievement, attention problems and internalizing problems (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Yang, Chen, Yen, & Chen, 2015). A major incidence of psychiatric disorders has been found during childhood, adolescence and also during adulthood in premature infants (Arpi & Ferrari, 2013; Lindström, Lindblad, & Hjern, 2009; Singh, Kenney, Ghandour, Kogan, & Lu, 2013; Treyvaud et al., 2013). Attention-deficit/hyperactivity disorder (ADHD) is a frequent disorder in these patients (Halmøy, Klungsøyr, Skjærven, & Haavik, 2012; Lindström, Lindblad, & Hjern, 2011; Strang-Karlsson et al., 2008; Treyvaud et al., 2013; Yang et al., 2015).

ADHD is a neurodevelopmental disorder affecting between 3% and 5% of the general population during childhood with a male-to-female ratio of 3:1 to 5:1 (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). The defining features of this disorder are inattention, impulsivity, and hyperactivity symptoms.

Premature birth has been associated with 2 and 5-fold increased risks of ADHD, being the inattentive subtype the most frequent ADHD subtype in very premature infants (Bhutta et al., 2002; Halmøy et al., 2012; Johnson et al., 2010; Lindström et al., 2011; Singh et al., 2013).

Several factors can explain the relationship between ADHD and prematurity, such as environmental causes, premature birth has been studied as risk factor for ADHD (Bhutta et al., 2002; Nigg, Nikolas, & Burt, 2010; St Sauver et al., 2004). It has been described that very premature birth has negative consequences on normal maturation processes in the brain, and immaturity may produce neurologic consequences and disruption in cortical development and brain connectivity (Inder, Warfield, Wang, Hüppi, & Volpe, 2005; Volpe, 2009). Also, premature infants early interact with hospital environment, medical treatments and external stimuli different from intrauterine environment. Therefore, they are exposed to stressful events in a crucial developmental stage which can contribute to structural and functional consequences in the brain development (Feldman, 2007). Not to be forgotten the social risk factors such as family dysfunction, social

adversity and parental psychopathology have also been related to both prematurity and as risk factors for ADHD (St Sauver et al., 2004; Vanderbilt & Gleason, 2010).

The majority of previous studies have reported associations between prematurity and attention deficits (Anderson et al., 2011; de Kieviet, van Elburg, Lafeber, & Oosterlaan, 2012; Heinonen et al., 2010; Jaekel, Wolke, & Bartmann, 2012; Perricone, Morales, & Anzalone, 2013) behavioral problems (Delobel-Ayoub et al., 2009; Samara, Marlow, Wolke, & EPICure Study Group, 2008; Scott et al., 2012) or reported ADHD symptoms (Brault & Lacourse, 2012; Elgen, Sommerfelt, Leversen, & Markestad, 2015b; Morales, Polizzi, Sulliotti, Mascolino, & Perricone, 2013; Strang-Karlsson et al., 2008; van Baar, Vermaas, Knots, de Kleine, & Soons, 2009; Visser et al., 2014). However, fewer studies have focused on clinical ADHD diagnosis.

Furthermore, previous researches have been carried out in several cultural populations (Chu et al., 2012; Lindström et al., 2011; Strang-Karlsson et al., 2008; Sucksdorff et al., 2015; Yang et al., 2015). In Spain, we found a study that showed the increase of ADHD medication use with no study of the diagnosis of ADHD(Raman et al., 2018). To our knowledge no studies have assessed the relation between prematurity and ADHD taking into account both, diagnosis or treatment of ADHD.

Aims of the study

The primary aim of the present study was to evaluate the association between prematurity and the risk of presenting ADHD (either by diagnosis or treatment) during childhood in a Spanish population. The secondary aims of the study were to assess this association according to (1) the gestational age (2) prematurity severity and (3) age of ADHD diagnosis and/or first pharmacological ADHD treatment.

Hypotheses

We hypothesized that prematurity is associated with a major risk of ADHD and patients with a lower gestational age and a severe prematurity have a higher risk of developing ADHD. Also, premature patients have a lower age on their ADHD initial diagnosis and first pharmacological ADHD treatment.

PATIENTS AND METHODS

STUDY DESIGN

We carried out a matched cohort study. Premature children were matched by age (+/- 2 months), sex and primary care center with children with no premature diagnosis registered at primary care.

The study protocol was approved by the Hospital Universitari Vall d'Hebron and by the IDIAP ethic research committees before any data extraction.

PARTICIPANTS

Premature children [(<37 gestational week (gw)] assisted in the Neonatal Intensive Unit from Hospital Universitari Vall d'Hebron (HUVH) which is a tertiary-level university-affiliated teaching hospital in Barcelona, reference hospital for premature births in Catalonia from 1995 to 2007 were selected as the premature cohort if they were alive at hospital discharge, they had a follow-up in a primary care centre from the Catalan Health Institute (ICS) with available medical health records.

Non-premature children (≥ 37gw) were selected from the SIDIAP database (Information System for the Development of Research in Primary Health Care) after exclusion of those with a premature related diagnosis (International Classification Diseases 10th ed: O60 "Preterm labour and delivery" and P07 "Disorders related to short gestation and low birth weight, not elsewhere classified") or or a gw <37 registered.

Data was analysed until 2013. Patients from both cohorts had to be active at the end of 2013 in order to have information regarding treatment and diagnosis related to ADHD.

DATA SOURCE

The HUVH provided administrative data of premature infants born between 1995-2007 in order to link these patients data to their data in SIDIAP.

Children assisted in primary care centers from the Catalan Health Institute ICS have data registered in the SIDIAP(SIDIAP, n.d.). SIDIAP database compiles data from 279 primary care teams of the ICS. It contains anonymized longitudinal medical records containing data on demographics, symptoms, diagnoses [(codified by the International Classification of Diseases, Tenth revision (ICD10)] (WHO, 2016), and prescriptions for 5.8 million people (>80% of the Catalan population, 15% of the Spanish population) with data from almost one million children. SIDIAP is linked with the pharmacy invoicing database provided by the National Health Service of Catalonia (Catsalut) and medications are recorded using the Anatomical Therapeutic Chemical (ATC) codes.

VARIABLES

a. Sociodemographic characteristics: age and gender.
b. Gestational age: for the premature cohort this variable contains 4 categories depending on the gw at birth: (1) 35-36 gw, (2) 33-34 gw, (3) 29-32 gw, (4) ≤ 28 gw. In the non-premature cohort: ≥ 37.
c. Prematurity severity: prematures whose corrected gestational age at the moment of medical discharge was higher than 40 gw.
d. Diagnosis of ADHD: patients who had registered one of the following diagnosis in their electronical clinical history according to the ICD-10: hyperkinetic disorder (F90), disturbance of activity and attention (F90.0), hyperkinetic conduct disorder (F90.1), other hyperkinetic disorder (F90.8), hyperkinetic disorder unspecified (F90.9).
e. Pharmacological treatment for ADHD: at least one prescription of a centrally acting sympathomimetic drug according to the Anatomical Therapeutic Chemical Classification System, ATC Code (N06BA group). This code includes methylphenidate (N06BA04) and atomoxetine (N06BA09).
f. Outcome of interest: ADHD: patients with a registered diagnosis of ADHD, as defined in d), or/and at least one prescription for ADHD treatment during the studied period, as defined in e) till the end of the estudy (2013).

STATISTICAL ANALYSIS AND SAMPLE SIZE

A sample size according to an incidence of 1.8% of ADHD diagnosis in the general population in Catalonia was calculated. Assuming an increased risk of 2% for ADHD in premature children, 1074 patients per

group are required to detect differences between premature and non-premature children with a power of 80% and probability of type I error of 5%.

Descriptive statistics were provided for baseline data of the two cohorts using mean and standard deviations for continuous variables and frequencies and percentages for categorical ones. Prevalence is defined as the percentage of children with ADHD (treated or diagnosed) at the end of the study (2013) regarding to the all the children included in the study. Incidence is estimated for year of age as the number of new cases (diagnosed or treated for ADHD) for every thousand children per age.

The Kaplan-Meier method was used to estimate the cumulative risk of ADHD and the comparison among different cohorts was performed using the log rank statistic stratifying by age. A Cox proportional-hazards model was fitted in order to estimate the hazard ratio (HR) between cohorts. All statistical analyses were performed using R version 3.2.5.

RESULTS

5,131 premature infants were discharged from the Neonatal Intensive Care Unit from HUVH born in the period 1995-2007. From these children 27.03% (n= 1387, 75.1%) were not assisted in primary care centers from the ICS, neither had their medical health records available. Then, a total of 3,744 premature infants were matched with 3,744 non-premature infants in the SIDIAP data base. Figure 1.

BASELINE CHARACTERISTICS

All premature and non-premature children were matched by age (+/- 2 months), sex (1,752 females, 46.8%) and Primary Care center. The mean age at the end of study was 11.7 years (SD 3.74). Among the children in the premature cohort 38% (n=1,423) were born between 35-36 gw, 28.9% (n=1082) between 33-34 gw, 915 (24.4%) between 29.32 gw and 8.65% (n=324) at 28th or under gw. For the non-premature cohort more than 50% did not have the gestational week registered. Table 1.

PREVALENCE AND INCIDENCE OF ADHD

A higher prevalence of ADHD was observed in the premature children at the end of the study (7.4% vs. 3.2%). Males presented a higher prevalence of ADHD (10.5% and 5.3%) than females (4.8% and 1.2%) in premature and non-premature cohorts, respectively (Figure 2)

The highest incidence of ADHD among premature children was at 8 years old (15.04 ‰) with another peak at 12 years (10.64 ‰), meanwhile the incidence among the non-premature children had several peaks, being the most marked at 9 and 13 years old (7.2‰ and 6.72‰ respectively) (Figure 3).

GESTATIONAL AGE AND ADHD

The cumulative risk of ADHD according to the gestational week is shown in figure 4.

There was a statistically significant higher risk of ADHD for the premature children (HR = 2.4, 95%CI from 1.9 to 3.0). Similar associations were found for ADHD diagnosis (HR = 2.2, 95%CI from 1.7 to 2.8) and for ADHD treatment (HR = 2.3, 95%CI from 1.8 to 3.0) Table 2. Stratifying by gw groups, the highest risk respect to the non-premature cohort was observed in the extremely premature newborns (HR= 5.57, 95%CI from 2.49 to 12.46), followed by the late premature newborns (HR= 1.70 95%CI from 1.19 to 2.44) (Table 4.)

PREMATURITY SEVERITY AND ADHD

Prematurity severity was considered for those prematures without hospital discharge after their (theoretical) 40 gw. Data was only available for a subcohort of 626 patients that were born between 2006-2007. Severe prematures had a higher statistically significant risk of ADHD (HR = 5.52, 95%CI from 1.73 to 17.62) being also statistically significant once adjusted by the gw (HR = 3.62, 95%CI from 1.31 to 9.99).

AGE OF ADHD DIAGNOSIS/PHARMACOLOGICAL TREATMENT

Among children with ADHD diagnosis, 61.2% had received pharmacological treatment (175/286) and among those patients with ADHD drug prescription, 61.4% (175/285) had ADHD diagnosis. Nevertheless, there is a trend to diagnose after the first drug prescription: in 109 (62.3%) out of 175 children with diagnosis and pharmacology treatment, the former was registered previously.

Patients of the premature cohort were diagnosed of ADHD in an earlier age (Mean= 8.71, SD= 2.93 vs. Mean=9.5, SD=2.99; p=.038). However, non-significant differences were found on the age of the first pharmacological treatment for ADHD [Premature cohort: M= 9.49; SD=2.8 vs. Non-premature cohort: Mean= 9.59, SD=3.15; p=.929].

DISCUSSION

Our study is the first, to our knowledge, evaluating the relationship between prematurity and the presence of a clinical ADHD diagnosis in a Spanish population. The results suggest that prematurity was associated with a major risk of presenting ADHD and an increased index of ADHD pharmacological treatment than the general population. According to this first hypothesis, similar results have been found in previous studies based on other cultural cohorts (Chu et al., 2012; Lindström et al., 2011; Strang-Karlsson et al., 2008) suggesting no differences between countries in this association. In relation to gender, males showed a higher risk to present ADHD than females, with a 2.77 increased risk. In the same line, previous investigations have found that male sex was associated with a higher risk for ADHD(St Sauver et al., 2004; Willcutt, 2012). It also has been suggested that boys are more susceptible to environmental adversity(Biederman, Faraone, & Monuteaux, 2002).

In relation to our second hypothesis, we found that patients with a lower gestational age and a severe prematurity showed a higher risk of presenting ADHD. Previous studies have reported that preterm infants (<37 weeks of gestation) and extremely preterm birth (<28 weeks of gestation) were associated with 1.3 and 5 fold increased risk of ADHD, respectively(Halmøy et al., 2012). Our study reported a 1.8 and 5.6 fold increased respectively.

Preterm infants born before the 35 gw have a close follow up during their development also enrolling some specific programs because of their increased risk of learning disabilities or behavioral problems(Bhutta et al., 2002). For those preterm infants that are close to term delivery (35-36 gw) this risk has not been well stablished. Our results shown a risk for those born 35-36 gw as well as in Finland (OR 1.41 1.12–1.78) but opposite to those of Rochester (USA), who found similar rates of ADHD prevalence in late prematures and term children without no risk of ADHD for the late preterm (OR 1.05, CI95% 0.64-1.73) (Harris et al., 2013; Sucksdorff et al., 2015). This is an important finding as these babies are normally followed up in Primary Care without any specific control.

The HR tends to increase as the gestational week decrease but it not in a sequentially way (as this is a matching analysis where each premature is matched to a non premature (table). It has to be taken into account the prevalence for the pairs prematurenon premature for each gw match, explaining that even if we have a higher percentage of ADHD in preterm of 29-32 gw (8.6%) than in preterm of 33-34 gw (6.6%), theirHOR is higher for the last group because the match pair in this group (33-34 gw) have a lower prevalence (2.3%) than the 29-32 gw group (3.5%).

Regarding our third hypothesis, we observed that premature infants had an earlier ADHD diagnosis. However, the age of the first pharmacological ADHD treatment in premature infants was similar than the term infant cohort. A possible explanation to this result is that a 17.5% of children with current ADHD do not receive pharmacological treatment (Visser et al., 2014). According to our study, 26-28% of patients with an ADHD diagnosis did not receive pharmacological treatment for their disorder. Previous studies have found that only 37% of children receive drug treatment in the first year after the initial diagnosis of ADHD(Lindemann et al., 2012). Indeed, clinical guidelines recommend that ADHD medication should be reserved for children in which other supportive interventions have failed (such as psychological interventions), reserving medication for more severe cases. Thus, ADHD medication is a quite valid indicator of the more severe cases of ADHD and several epidemiological studies on ADHD have used data from medication registers as an indicator on ADHD incidence (Brault & Lacourse, 2012; Halmøy et al., 2012; Hodgkins, Sasané, & Meijer, 2011; Lindemann et al., 2012; Lindström et al., 2011; McCarthy et al., 2012; Silva, Colvin, Hagemann, & Bower, 2014).

There are some limitations to this study. Firstly, our study did not include the clinical evolution of the preterm, maternal history or socioeconomic factors that can be also associated to the development of ADHD (Sagiv, Epstein, Bellinger, & Korrick, 2013; Silva et al., 2014; St Sauver et al., 2004). Secondly, we could not obtain data relating the subtypes of ADHD, however a study showed that ADHD subtype can change within patients over time (Willcutt et al., 2012). Thirdly, in primary healthcare databases, patients can be identified as having a diagnosis only if they seek pharmacology treatment and we did not seek for other mental disorders that can be related to ADHD as oppositional defiant disorder, conduct disorder or learning disabilities among others and also be treated with ADHD drugs. Patients who receive a treatment not covered by the insurance cannot be identified in the primary care database. Therefore, no overestimation of the ADHD diagnosis has to be expected, as in Spain the pharmacologic treatment for ADHD is covered by the national health system. Furthermore, our study included adolescents, an age range that is often unlikely to seek treatment for mental health difficulties, suggesting that community prevalence is higher than treatment records indicate. In the SIDIAP data base not all the considered as non prematures had their gw registered (only 41.3%), what could be translated into data from some preterm infants wrong classified as non-pretematures.

We did not analyze the association between low birth weight (LBW) and ADHD, or adjusted our results by the LBW, even if results in this field are controversial, as well as for Apgar score, that when less than 8 at

5 min has been associated with a higher risk of using medication for ADHD(Lindström et al., 2011)·(Scott et al., 2012).

Therefore, our results on the risk of presenting ADHD in preterm infants are conservative. It is known that the inattentive subtype of ADHD is the most prevalent in premature infants, but individuals with the combined type are more likely to be referred for clinical services and to be diagnosed before(Willcutt, 2012). Additionally, ADHD in preterm children may differ qualitatively from ADHD in the general population, with less comorbidity with conditions such as conduct disorder(Johnson et al., 2010). This could also influence the rates of consultation. Another reason is that the median age of ADHD diagnosis during childhood is estimated to be at 6.2 years,(Visser et al., 2014) being infrequent the diagnosis in preschool children (such as 4 years). Such age was also included in the current study, probably making the results more conservative.

Despite these limitations, the current study included a population-based design with a large cohort and data collected using an extensive database, covering primary health centers of the public health system in Catalonia. Indeed, the study was based on clinical diagnosis of ADHD, differently from other studies where diagnosis of ADHD and prescribed medications were provided by parents(Brault & Lacourse, 2012; Visser et al., 2014) or screening tests(Elgen, Sommerfelt, Leversen, & Markestad, 2015a). In our study, diagnoses were provided by physicians, so ADHD symptoms were not subject to reporting bias as are parental reports.

CONCLUSION

The findings of this report have several important clinical and public health implications. Early development is a particular period of vulnerability but also plasticity(Sonuga-Barke & Halperin, 2010). Thus, an early identification and treatment of hyperactivity/impulsivity and inattention trajectories during preschool age in premature infants could prevent later difficulties in adolescence and adulthood(Galera et al., 2011; Lindström et al., 2009). Future specific programs could be developed to enroll late preterm and early term infants during their follow up while childhood and adolescent.

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