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Age at first febrile seizure correlates with perinatal maternal emotional symptoms

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ABSTRACT

Objective: Prenatal exposure to stress and fever are factors lowering seizure threshold in animal models. The fever effect on seizure threshold is well documented in human infants, however the associations between maternal perinatal stress and infants' susceptibility to seizures is unknown. This is the first study in humans to investigate longitudinally, whether in humans, the effect of maternal perinatal emotional symptoms such as stress, anxiety and depression that may trigger a biological stress response on age at first seizure occurrence.
Method: The study sample is a subgroup drawn from a longitudinal follow up cohort (3D cohort study: Design, Develop, Discover, $N = 2366$ mother-infant dyads). Twenty-nine otherwise healthy infants who had a febrile seizure (FS) episode before the last follow-up visit (around 24 months of age) were studied. Mothers completed questionnaires regarding their emotional health at each pregnancy trimester and at three months postpartum. The link between maternal emotional symptoms and infant age at first FS was assessed through correlations and multiple regressions.
Results: We found that maternal anxiety symptoms during the second trimester of pregnancy are linked to the age at first FS ($r(23) = -0.459$, $p = 0.021$) and explain 21.1% of its variance. Postnatal maternal depression symptoms at 3 months postpartum were also associated with the age at first FS ($r(23) = -0.587$, $p = 0.002$) and explained an additional 17.6% of variance. Together, the variables explained 38.7% of the variance in age at first FS. Maternal perceived stress symptoms at 3 months postpartum were also linked to the age at first FS ($r(23) = -0.418$, $p = 0.038$), however, stress did not significantly contribute to the variance of age at first FS..
Significance: Our results suggest a link between increased perinatal maternal emotional symptoms and the age at first FS. An earlier age at first FS may be the manifestation of a lower seizure threshold. Early first seizure occurrence is a risk factor for compromised neurological and cognitive development. Further studies should address the mechanisms by which perinatal maternal emotional symptoms may have an impact on seizure threshold in humans.

Abbreviations: FS, febrile seizures; GA, gestational age; SES, socio-economic status

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1. Introduction

FS are the most common form of seizures in children (2% to 5%), with a peak prevalence during the second year of life (Verity et al., 1985; American Academy of Pediatrics, 2011). They occur in febrile infants with no history of spontaneous seizure or neurological insults (American Academy of Pediatrics, 2011). Studies suggest that fever leads to enhanced neuronal excitability and lowers the seizure threshold (Heida et al., 2009). The exact pathophysiology of FS is unclear and probably multifactorial. General outcome following FS is generally favorable, however it is a sign of seizure susceptibility in infants who are otherwise healthy. While longer FS duration (i.e. over 15 min) is the principal risk factor for negative consequences following FS (American Academy of Pediatrics, 2011; Hesdorffer et al., 2011), earlier FS occurrence is also a factor influencing prognosis. It predicts seizure recurrence and future complex features (e.g. longer FS duration) which have an impact on both cognitive and neurological prognosis (Annegers et al., 1987; Elger et al., 2004; Hesdorffer et al., 2011; Roy et al., 2011). As age at first seizure occurrence is an important characteristic in patient seizure history, knowledge regarding factors underlying the age at first FS could lead to a better understanding of factors affecting seizures' genesis and frequency. Furthermore, it could positively influence the prognosis following FS.

Current hypotheses drawn from animal studies posit that perinatal stress can facilitate seizures by enhancing neuronal excitability and lowering seizure threshold (Edwards et al., 2002; Koe et al., 2014; van Campen et al., 2016, 2014). Biological stress, especially during sensitive developmental periods, can have long-lasting effects on brain excitability by inducing anatomical alterations as well as changes in both neurotransmitter and hormone levels (Baram and Hatalski, 1998; Dube et al., 2015; Hollrigel et al., 1998; MacKenzie and Maguire, 2015). Consequently, exposure to biological stress during the prenatal and postnatal periods increases seizure vulnerability and severity, and can lead to a younger age at first seizure (Edwards et al., 2002; Koe et al., 2014; van Campen et al., 2014). Interestingly, animal studies show that in rats with a genetic predisposition to epilepsy reducing early life environmental stress can delay but cannot prevent seizure onset (Leussis and Heinrichs, 2009).

Although stress related symptoms, especially anxiety, are well known seizure precipitant in humans (Privitera et al., 2014), human studies addressing the link between perinatal stress and seizures are sparse. Prenatal stress does not seem to impact FS incidence (Li et al., 2009), but familial emotional stress increases FS incidence in toddlers (Aydemir and Bedir, 2010). The link between perinatal stress and the age at first FS has never been examined. Nevertheless, human studies show that perinatal exposure to biological stress leads to a variety of consequences (Glover, 2015; King et al., 2012). Prenatally, it influences infant neurodevelopment through biological mechanisms (Lupien et al., 2009) and can lead to a variety of consequences depending on timing of exposure (King et al., 2012). Postnatally, maternal symptoms of stress and depression further impact the infant's stress response through inadequate coping mechanisms (Apter-Levi et al., 2016). Furthermore, perinatal exposure to stress related symptoms creates lasting changes in stress responsiveness itself, meaning that subsequent stress reactions are different compared to those of control subjects (Joëls et al., 2012).

Drawing from previous studies, we posit that perinatal exposure to maternal symptoms triggering a biological stress response are linked to an altered physiological stress response in infants, such as perinatal maternal symptoms of stress, anxiety, or depression (Apter-Levi et al., 2016; Bhagwagar et al., 2005; Lupien et al., 2009; OConnor et al., 2013O'Connor et al., 2013). Thus, exposure to maternal symptoms of stress, anxiety or depression may have an impact on infant seizure occurrence as shown by changes in the age at first seizure. Using a subgroup from a longitudinal study, we focussed on FS because they are the most common seizures in children with first occurrence and peak prevalence early in life (Verity et al., 1985). Thus, focusing on FS facilitates the acquisition of longitudinal data and may provide a larger sample. To our knowledge, this is the first prospective study focusing on the relationship between perinatal stress and age at first FS in humans. We hypothesized that exposure to higher levels of perinatal maternal symptoms would be associated with a younger age at first FS.

2. Material and methods

2.1. 3D cohort study participants

This research project is a substudy of the large-scale longitudinal 3D (Design, Develop, Discover) cohort study of the Integrated Research Network in Perinatalogy of Quebec and Eastern Ontario (IRNPQEO), from which two subgroup of participants were drawn. The 3D cohort study aims at creating a bank of data and samples targeting child development and parental health. Since this project targeted issues such as adverse exposure during pregnancy, the exclusion criteria were maternal current intravenous drug use, severe illnesses or life threatening conditions (e.g. cancer, epilepsy) and multiple births.

2.2. Procedures

Participants were recruited from nine urban clinical centers in three metropolitan areas in the province of Quebec (Canada), accounting for more than half of the population of Quebec. Of the 9864 women approached, 6348 met eligibility criteria and 2456 agreed to participate. Forty-seven women were determined to be ineligible and 43 withdrew from the study. Thus, 2366 pregnant women, between 18 and 45 years of age, participated in the study (Fig. 1) (Fraser et al., 2016). The most common reasons for ineligibility included women that were not in the

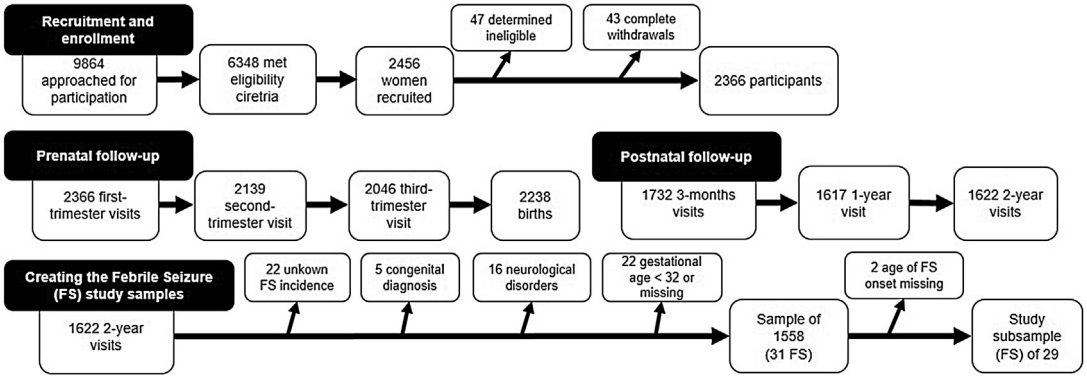

Fig. 1. Patient flow diagram.
Description: Patient flow diagram for the 3D cohort study recruitment and follow-up visits, and for the creation of the subsamples for the current study. The figure was adapted from Fraser et al. GA = Gestational Age; FS = Febrile Seizures.