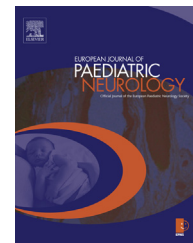




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Original Article

Association between iron deficiency and febrile seizures



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ABSTRACT

Objective: The relationship between iron status and febrile seizures has been examined in various settings, mainly in the Developing World, with conflicting results. The aim of this study was to investigate any association between iron deficiency and febrile seizures (FS) in European children aged 6–60 months.

Design: Prospective, case–control study.

Setting: Greek population in Thessaloniki.

Patients: 50 patients with febrile seizures (cases) and 50 controls (children presenting with fever, without seizures).

Interventions: None.

Main outcome measures: Haematologic parameters (haemoglobin concentration, haematocrit, mean corpuscular volume, red cell distribution width), plasma iron, total iron-binding capacity, plasma ferritin, transferrin saturation and soluble transferrin receptors were compared in cases and controls.

Results: Plasma ferritin was lower (median [range]: 42.8 (3–285.7) vs 58.3 (21.4–195.3 ng/ml; $p = 0.02$) and Total Iron Binding Capacity (TIBC) higher (mean [Standard Deviation] 267 [58.9] vs 243 [58.45] $\mu\text{g/dl}$, $p = 0.04$) in cases than in controls. Results were similar for 12 complex FS cases (ferritin 30 (3–121 vs 89 (41.8–141.5 ng/L; TIBC 292.92 [68.0] vs 232.08 [36.27] $\mu\text{g/dL}$). Iron deficiency, defined as ferritin <30 ng/ml, was more frequent in cases (24%) than controls (4%; $p = 0.004$). Ferritin was lower and TIBC higher in 18 with previous seizures than in 32 with a first seizure although haemoglobin and mean cell haemoglobin concentration were higher.

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Conclusions: European children with febrile seizures have lower Ferritin than those with fever alone, and iron deficiency, but not anaemia, is associated with recurrence. Iron status screening should be considered as routine for children presenting with or at high risk for febrile seizures.

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1. Introduction

Febrile seizures (FS) are the most common type of seizures in children (2–5%).^{1–3} FS, although frightening to caregivers, are benign, and the risk for epilepsy following an episode of simple FS is no greater than that of the general population.⁴ There is a substantial literature examining risk factors including: positive family history for FS or epilepsy,⁵ maternal smoking or alcohol consumption during pregnancy,⁶ herpes type 6 or 7 infection⁷ and nutritional deficiencies including zinc⁸ and iron.⁹ Iron plays a critical role in the metabolism of several neurotransmitters as well as in myelination^{10–12} and deficiency is associated with a number of neurological conditions in children including developmental delay, stroke, breath-holding attacks and cranial nerve palsies.^{11,12} Iron deficiency (ID) might therefore lower the seizure threshold¹⁴ but there is controversy over whether there is an association with FS,^{9,13–24} most conducted in the Developing World.²⁴ In this study we investigate whether there is any association between ID and occurrence of FS in Greek preschoolers.

2. Patients and methods

The present study is a prospective, case-control study following patients from March 2009 to March 2011. Consecutive children with FS (simple and complex) admitted to the 1st Pediatric Clinic, “Hippokratio” General Hospital, Thessaloniki, Greece, aged 6–60 months were considered for inclusion in the study. A total of 50 children with FS (cases) were enrolled. A reference group of 50 children (controls) were selected among children hospitalized for a febrile illness, but without seizures. Controls were matched to cases on gender and age (6–60 months). Exclusion criteria were: age <6 months or >60 months, history of afebrile seizures, any anti-epileptic drug usage, history of serious head trauma or central nervous system infection, chronic disease and neurologic deficit or developmental delay. The University's Ethics review board approved the use of human subjects and written informed consent was obtained from parents or legal guardians.

For each case and control a thorough personal history was taken. Information on the perinatal period included gestation, type of delivery (caesarian section or vaginal), birth weight, smoking or alcohol consumption during pregnancy and perinatal problems. Personal history documented included: breastfeeding duration, vaccination status, history of various illnesses, number of febrile episodes per year, previous surgeries,

past admissions to hospital, history of head trauma, any drug usage and developmental milestones. Details regarding family history were obtained as to presence of hereditary disease and/or positive history for febrile and afebrile seizures.

FS were defined according to the National Institute of Health consensus statement² and categorized as simple or complex.³ Simple FS were generalized, lasting <15 min, occurring only once in 24 h and not provoking any neurological abnormality after the episode, in an otherwise neurologically healthy child. FS were complex if they were focal, of longer duration (>15 min), occurred more than once in 24 h and/or caused neurologic deficit (such as Todd's paralysis). FS or multiple episodes of FS lasting >30 min without the patient gaining consciousness in the meantime were defined as Febrile Status Epilepticus (FSE).³

Morning venous blood samples were collected from all cases and controls for Haemoglobin, Haematocrit, Mean Cell Volume (MCV), red cell distribution width (RDW), plasma iron, total iron binding capacity (TIBC), plasma ferritin, soluble Transferrin factor Receptor (sTfR) and transferrin saturation, during the first 3 days of fever. Haemoglobin, Haematocrit, MCV and RDW were part of a complete blood count (Abbott analyzer, Cell Dyn 3700). Plasma iron and TIBC were measured by using Olympus Medicon AU2700 analyzer. Transferrin saturation was calculated using the formula: (plasma iron/TIBC)×100. Plasma ferritin was measured using an immuno-enzyme method with microparticles (AxSym System, Abbott). For the quantitative measurement of sTfR the enzyme-linked immunosorbent (ELISA) assay was used (Quantikine, R&D systems, Minneapolis, MN). Anaemia was defined as haemoglobin levels ≤10.5 g/dl for children 6–24 months and ≤11.5 g/dl for children 24–60 months (22, own unpublished data). ID was defined as plasma ferritin levels ≤30 ng/ml, in the context of a febrile-infectious disease.²⁵

All continuous variables (e.g Haemoglobin, MCV) were compared among cases and controls using independent t-tests unless the data were skewed data when the Mann–Whitney test was used, while categorical variables were compared using χ^2 . Statistical significance was set at $p \leq 0.05$. Statistical analysis was performed with use of the Statistical Package for the Social Sciences (SPSS) (PASW 18.0).

3. Results

3.1. Demographics

There were a total of 50 cases and 50 controls; there were no differences in age or gender (Table 1). Among the 50 cases,

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