Factors associated with febrile seizures occurence in tunisian children

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ABSTRACT

Objective : We aimed to identify the factors associated with febrile seizures (FS) occurrence.

Methods : This was a case-control study. Sixty cases of FS were prospectively recorded and compared to 60 controls admitted for fever without seizures. Baseline Data were collected from all consecutive patients and laboratory haematological parameters including complete blood count, serum iron, serum ferritin and zinc levels were performed prospectively the first day of admission. The two groups were compared to identify parameters associated with FS occurrence. All statistical analysis was performed with SPSS software, version 19.

Results : The mean age was 18±12.7 months in cases and 20±13.9 months in controls. The consanguinity rate was significantly higher in cases than in controls (p=0.028). A positive family history of febrile seizures was found in 22 cases (36.7%) which was statistically significant as compared to controls (p=0.003).
In contrast, there was no significant statistical difference noted when considering the positive family history of epilepsy (p= 0.43). Gestational age, weight birth and breastfeeding duration were significantly lower in cases (p= 0.002, 0.023 and <0.0001 respectively). Similarly the duration of fever was lower in cases group (10.7±17.4 vs 35.6±18.4 hours, p <0.001). Mean haemoglobin, serum iron, ferritin and zinc were significantly lower in cases than controls. Multivariate analysis identified four factors associated with FS occurrence : family history of FS, duration of breast-feeding less than 6 months, rapid rise of body temperature and iron deficiency anaemia.

Conclusion : in children with personal or family history of FS. Clinicians should particularly incite breastfeeding and prevent micronutrient deficiencies, especially iron deficiency.

Keywords : Febrile seizure; Childhood; Prophylaxis; Epilepsy; Anemia.

INTRODUCTION :

Febrile seizures (FS) are defined by the National Institute of Health as convulsions that occur in children between three months and five years of age triggered by fever, without evidence of intracranial infection or defined cause [1]. The definition of the International League Against Epilepsy (ILAE) is very similar, differing only in the lower age limit which is one month [2]. FS are the most common type of childhood seizures generating high healthcare costs. Despite their benign nature, they can be extremely frightening for parents. Otherwise, the primary prevention measures of these frequent events cannot be conducted since the exact causes are still unknown, although some studies indicate a possible association with environmental and genetic factors. In this context, we aimed to study the risk factors associated with FS occurrence.

METHODS :

We prospectively performed a single centre case-control study between January and December 2018. The case group included all children hospitalized for FS in the department C at the Children's Hospital of Tunis during the study period. We did not include patients with history of perinatal period complications such as bleeding, difficult labour or low APGAR score, children born less than 34 weeks gestation and those with mental retardation or epilepsy and subjects with evidence of other definite causative diseases, such as central nervous system infection or metabolic abnormality. For each patient we included a subject control of the same age and gender hospitalized for acute fever without convulsions during the same period. Data collected included age, gender, history of consanguinity, family history of FS or epilepsy, gestational age, birth weight, breastfeeding duration, vaccination

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status. Clinical parameters included also anthropometric parameters, central temperature measured at the admission. We specified seizure types and duration, duration and cause of fever. For each patient, we carried out the following biological parameters: complete blood count, serum iron, serum ferritin, and serum zinc. Written informed consent was obtained from all parents of children included in the study. All analyses were performed using SPSS software version 19.0. We compared categorical variables with chi-square test or Fisher's exact test and continuous variables with the student t test. In all statistical tests, the significance level was set to 0.05. Univariate odds ratio was calculated as an approximation of relative risk factors by simple cross-tabulation, with 95% confidence intervals (95% CI). We have transformed the quantitative variables into categorical variables. To determine the threshold at which it must "cut", we have established ROC (Receiver Operating Characteristics) curve. After verifying that the area under the curve was significantly > 0.5, we have chosen the threshold value of the variable as corresponding to the best couple "sensitivity-specificity. In order to identify risk factors independently related to the event, we conducted a logistic regression analysis in descending order.

METHODS :

A total of 120 patients were included in the study. There were 60 children admitted for FS and 60 controls. The ratio male to female was 1.5 in cases and 1.85 in controls without significant difference (p=0. 57). The mean age was 21.4 ± 12.7 ranging from 6 to 60 months in FS group and 24.9 ± 13.9 months (range 7- 60 months) in controls (p= 0.15). Among the cases, 47 (78.3%) children had simple FS, and 13 (21.7%) had complex FS. The consanguinity rate was significantly higher in cases than in controls (58.3% versus 38.3%, p= 0.028, OR= 2.25, 95 % CI= 1.08-4.67). A positive family history of febrile seizures was found in 22 cases (36.7%) and 8 controls (13.3%) (p= 0.003, OR= 3.76, 95 % CI= 1.51-9.34). In contrast, there was no significant difference between the two groups with regard to the positive family history of epilepsy (p= 0.43) (table1).

Tableau I : Comparison of baseline characteristics parameters in the two groups.

Variable	Total population (N= 120)	Febrile seizures group (N=60)	Control group (N=60)	p
Mean age ± SD (months)	23.16 ± 13.38	21.42 ± 12.72	24.9 ± 13.90	0.15
Ratio (Male/ female)	1.66	1.5	1.85	0.57
Consanguinity rate(%)	48.3	58.3	38.3	0.028
Family history of FS (%)	25	36.7	13.3	0.003
Family history of epilepsy(%)	14.2	16.7	11.7	0.43
Preterm birth (%)	26.7	13.3		0.068
Mean gestational age ± SD (Weeks)	37.24 ±2.2	36.6 ± 2.3	37.9 ±1.9	0.002
Birth weight ± SD (grams)	3132 ± 817	2960 ±781	3300 ± 823	0.023
Breast feeding duration ±SD (months)	8.3 ± 6.2	5.95 ± 50	10.63 ±6.4	$<10^{-3}$

FS : Febrile seizures ; SD : Standard deviation ;

Sixteen cases and eight controls were premature at birth and the mean gestational age was of 36.6±2.3 and 37.9±1.9 weeks respectively in cases and controls (p= 0.002). Likewise, the birth weight was significantly lower in cases (2960 ±780 versus 3300 ± 820 grams, p= 0.023). Concerning breastfeeding, it was more common and of longer duration in the control group. Indeed, the mean duration of breastfeeding was 10.63 ± 6.4 months in controls versus 5.95± 5 months in cases (p <10-3). Of these, 38 children were breast-fed for less than 6 month versus 17 controls (p <10-3). Otherwise, vaccination status was similar in both groups. The duration of fever was significantly lower in the case group (10.7 ± 17.4 versus 35.6 ± 18.4 hours, p<10-3). Paracetamol intake prior to admission was significantly more common in patients (45 versus 18; p<10-3, OR= 0.14, 95% CI= 0.06-0.32). Similarly, anti-inflammatory drugs intake was more common in the case group (36 versus 11; p <10-3, OR= 0.15, 95% CI= 0.06-0.34). On physical examination, z-score height-for-age was between -2 and +2 standard deviations (SD) in all cases and controls. Z-score weight-for-age was normal in 58 cases and below -2 SD in 2 cases. It ranged between -2 and +2 SD in 56 children and was below -2 SD in 4 children in the control group (p = 0.8). Viral infection was the most common cause of fever in both groups (50.8%), followed by Ear, Nose and Throat infections (32.5%), urinary tract infection (9.2%), and respiratory infection (7.5%). There was no significant difference between the two groups regarding the origin of fever (p= 0.40). The mean hemoglobin level was of 9.43±1.67 in cases versus 10.45 ± 1.57 in controls (p=0.001). All the same, serum iron and serum ferritin were significantly lower in cases than controls (table 2). Serum zinc levels were significantly higher in control subjects (10.96 ± 2.22 versus 12.75 ± 2.28 µmol/L, p= 0.004).

Tableau II : Comparison of biological parameters in the two groups.

Variable	Febrile seizures group	Control group	P-value
Hemoglobin (g/ dL)	9.43 ± 1.67	10.45 ± 1.57	0.001
MCV (fl)	65.86 ± 10.57	71.23±6.50	0.001
MCH (pg)	23.01 ±4.45	25 ± 3.73	0.009
MCHC (g/dL)	28.23 ±4.41	30.35 ±3.56	0.005

Platelet count (cells/mcL)	29.45 ± 141	234.18 ± 100	0.011
Leukocytes count (cells/mm3)	10586.67 ± 40	9856.67 ± 35	0.295
Serum ferritin (ng/mL)	24.3 8± 24.59	52.36 ± 35.14	$<10^{-3}$
Serum iron (µmol/L)	10.77 ± 10.59	16.26 ± 9.15	0.003
Serum zinc (µmol/L)	10.96 ± 2.22	12.75 ± 2.28	0.004

MCV: mean corpuscular volume, MCH: Mean Corpuscular Hemoglobin, MCHC : Mean Cell Hemoglobin Concentration .

Independent risk factors for FS (multivariate analysis) were family history of FS, duration of breast-feeding less than 6 months, duration of fever less than 6 hours before admission and iron deficiency anemia (table 3).

Tableau III : Independent risk factors for Febrile seizures in multivariate analysis.

	Case group	Control group	AOR	95% CI	p
Breast feeding <6 months	38 (63.3%)	16 (26.7%)	9.56	2.47-36.9	0.001
Fever duration <6 hours	35 (58.3%)	5 (8.3%)	14	3.55-55.7	$<10^{-3}$
HB <10 g/dL	29 (48.3%)	15 (25%)	5.64	1.23 - 25.6	0.025
Serum ferritin <22 µg/L	45 (75%)	17 (28.3)	27.57	5.7-133	$<10^{-3}$
Serum zinc <10 µmol/L	12 (20 %)	2 (3.3%)	5.83	0.65 - 51.76	0.114
Family history of FS	22 (36.7%)	8 (13.3%)	5.5	1.4 - 21.5	0.014

AOR : Adjusted Odds Ratio, CI: Confidential interval

DISCUSSION :

Despite its predominantly benign nature, FS is a scary experience for most parents. It occurs when a susceptible child of a critical age has a fever. Any viral or bacterial illness may provoke FS. In the present study, FS occurrence was associated with Family history of FS, short breastfeeding duration, rapid increase in body temperature and iron deficiency anaemia. In our series, family history of FS was associated with FS occurrence in childhood. Febrile seizures are known to aggregate in families. Genetics seem to play a major role in FS. Family history of FS is reported with the percentage of 20 to 55 % in children with FS As many as 25% to 40% of children with febrile seizures have a family history of FS [3-7]. The role of genetic factors in the occurrence of FS is currently well recognized and documented. Family studies have demonstrated the high genetic susceptibility to febrile seizures and have identified multiple gene variations responsible for this condition [8, 9]. In opposition to our results, some authors consider familial epilepsy as a risk factor for FS occurrence [10, 11]. Prematurity and low birth weight have been reported as risk factors for FS by several authors [7, 12]. In reality, it is difficult to study the relationship between the birth term and the occurrence of FS because premature infants may have infra-clinical neurological lesions and even non-detectable by cerebral imaging and it is thus difficult to make the diagnosis of FS in these children. Despite the non-inclusion of very premature infants in our study, the mean birth term was significantly lower in the case group. Similarly, control children had a significantly higher birth weight. However, the two above mentioned parameters were not independent risk factors for FS occurrence at multivariate analysis. Otherwise, there is little data concerning the preventive effect of breast-feeding on occurrence of FS. In an Iranian case-control study published in 2010, mean duration of breastfeeding was significantly lower in febrile controls without convulsion (p <10-3) [13]. However, this study compared the two groups without controlling the confounding effects. The breastfeeding protective effect found in our series, has been reported by other authors [13, 14]. Thus, it could be suggested that exclusive breastfeeding during the first six months of life protect children from FS occurrence. In fact, the high levels of polyunsaturated fatty acids such as arachidonic acid and docosahexaenoic acid, cholesterol and sialic acid in the Breast milk plays an important role in brain development and stabilization of neuronal membranes and may increase the threshold of seizures. In addition, it is evident that gastroenteritis and respiratory infections are much less common in breastfed children, with a low possibility of developing fever. The majority agrees that the rapidity of fever set-up increases the risk of developing FS [15, 16]. However, the methodology is not detailed in most of these studies. Several data are often unclear: the temperature measurement technique (axillary or rectal), the temperature measurement time (before or after the crisis) and the location of the temperature measurement at the home or emergencies. Similarly, the measures taken and the antipyretic treatment are not mentioned in all the above studies. In the present study, we compared the rectal temperature measured at the time of admission between the two groups.

Using multivariate analysis, we found that fever duration less than 6 hours multiplies the risk of FS occurrence by 14. Otherwise, as reported in the literature [17], viral infections were the first cause of fever in our patients. In our study, iron deficiency anemia was a risk factor for FS occurrence. Indeed, iron is important for the function of various enzymes and neurotransmitters in the central nervous system. Thus, an iron deficiency can decrease the threshold of convulsions. A prospective case-control study, with a methodology close to ours, investigated the association between iron deficiency and CF by comparing two groups of children aged 6 months to 5 years admitted to a pediatric emergency department in southern Iran between March 2007 and January 2009. Iron defi-

ciency was more frequent in children with FS [18]. These results are consistent with those reported by meta-analysis published in 2014 [19]. Another meta-analysis enrolling 2416 children with FS and 2387 controls showed that iron deficiency anaemia was significantly associated with FS (OR= 1.98) [20]. Finally, we note that we prospectively conducted the first study in our country with the objective of identifying the clinical and biological parameters associated with FS occurrence. This could serve as a basis for carrying out preventive actions. However, the sample size was too small. Thereby, our results should be supported by other larger scale and multicenter studies.

CONCLUSION :

Despite its benignity, febrile seizures still frightening for parents. They represent a common cause of consultation and hospitalization. Genetic susceptibility for FS occurrence is currently admitted worldwide. Identifying risk factors associated with FS could offer a basis to prevent this condition and reduce its frequency. Based on our results, clinicians should support and promote breastfeeding and prevent micronutrient deficiencies, especially iron deficiency in children at risk for FS occurrence .

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Ethics approval and consent to participate : Written informed consent was obtained from all parents of the patients.

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