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Low Iron Status: A Possible Risk Factor For First Febrile Seizure

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Abstract:

Background: Febrile seizure is a common cause of seizure in young children, with an excellent prognosis. Febrile seizures typically occur relatively early in an infectious illness, usually during the raising phase of the temperature curve. Rectal temperatures at this time may exceed 39.2oC, and approximately one-fourth of seizures occur at a temperature above 40.2oC. Despite the implicit relationship between fever and seizure activation, temperature itself probably does not lower the seizure threshold. The incidence of febrile seizures does not increase in proportion to temperature elevation, and febrile seizures are uncommon in the later stages of persistent illness.

Aim & Objective: To study the association between iron deficiency and the first febrile seizure.

Methods: This cross-sectional observational study was done with healthy Babies delivered and admitted to the inpatient postnatal ward of the department of pediatrics in Vydehi Institute of Medical Sciences And Research Center, Bangalore, during the study period (January 2015 – May 2016). For this 2ml of blood was collected into vacutainers through venipuncture under strict aseptic precautions. The serum is separated from cells by centrifugation. The assay is based on microplates coated with highly specific anti-ferritin-human antibodies. During the procedure, the binding of the analyte, as well as the formation of the sandwich complex and enzymatic color reaction take place during three different reaction phases.

Results: Thus the mean serum ferritin, HB, and MCV are found to be signed on the lower side among children with febrile seizures when compared to the children who did not have febrile seizures, which is statistically significant. Even though the MCH is less among children with febrile seizures it did not achieve statistical significance. The number of children with hemoglobin <11gm/dl is 51 (80.9%) in the febrile seizures group whereas among controls it is only 19 (30%) (P=0.00).*The Mean Corpuscular Volume <70fl is seen in 23 (36.5%) cases, whereas in controls it is only 8 (12.7%) (P= 0.003). Odds of children with febrile seizures having low Mean Corpuscular Hemoglobin is 1.1 when compared to those who did not have febrile seizures which is not statistically significant OR (95%CI) = 1.1(0.4-3)

Conclusion: There is a lower value of hematological indices like mean Hemoglobin, Mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration and Serum Ferritin in the cases group compared to the control group but no statistically significant difference. Iron deficiency stimulates the function of neurons and, consequently, increases the risk of convulsions. Similar conditions are observed in Attention Deficit Hyperactivity Disorder (ADHD) and Restless Leg Syndrome (RLS).

Keywords: Febrile, Children, Iron deficiency anemia.

Introduction:

A seizure or convulsion is a paroxysmal, time-limited change in motor activity and/or behavior that result from abnormal electrical activity in the brain. Seizures are common in the pediatric age group and occur in approximately 10% of children. Most seizures in children are provoked by somatic disorders originating outside the brain, such as high fever, infection, syncope, head-trauma, hypoxia, toxins, or cardiac arrhythmias. Other events, such as breath-holding spells and gastroesophageal reflux, can cause events that simulate seizures.[1] A few children also exhibit psychogenic seizures of psychiatric origin. Less than one-third of seizures in children are caused by epilepsy, a condition in which seizures are triggered recurrently from within the brain. [2] For epidemiological classification purposes, epilepsy is considered to be present when two or more unprovoked seizures occur at an interval greater than 24 hr apart. The cumulative lifetime incidence of epilepsy is 3% and more than half of cases begin in childhood. However, the annual prevalence of epilepsy is lower (10.5—0.8%) because many children outgrow epilepsy. [3] Although the outlook for most children with symptomatic seizures or those associated with epilepsy is generally good, the seizures may signal a potentially serious underlying systemic or central nervous system (CNS) disorder that requires thorough investigation and management. For children with epilepsy, the prognosis is generally good, but 10—20% have persistent seizures refractory to drugs, and those cases pose a diagnostic and management challenge. Seizures have been recognized since ancient times and although improvement has been made in management over this century compared to the previous 2000 years, there are still far too many children whose lives are crippled by poorly controlled seizures. [4] Infants and children are more prone to have seizures than adults. This appears to reflect greater neuronal excitability at certain ages as the excitatory glutamate system and inhibitory gamma aminobenzoic acid (GABA) system do not always balance each other.[5] This also results in the tendency to exhibit symptomatic seizures related to high fever, virus infection, minor asphyxia, medication, bacterial toxins, and biochemical upsets such as hypo- or hypernatremia and hypocalcemia.[6] Childhood seizure differs from adult seizure since the brain is a developing organ. The clinical picture is not static and the pattern of fits may change with age, e.g. infantile spasms can evolve into Lennox—Gastaut syndrome. Although precise mechanisms of seizures are unknown, several physiologic factors are responsible for the development of a seizure. [7] To initiate a seizure, there must be a group of neurons that are capable of generating a significant burst discharge and a GABAnergic inhibitory system. Seizure discharge transmission ultimately depends on excitatory glutamatergic synapses. Evidence suggests that excitatory amino acid neurotransmitters(glutamate, aspartate) may have a role in producing neuronal excitation by acting on specific cell receptors. Seizures may arise from areas of neuronal death, and these regions of the brain may promote the development of novel hyperexcitable synapses that can cause seizures.[8] Febrile seizures typically are associated with common childhood infections, most frequently upper respiratory tract, middle ear, and gastrointestinal, that are viral. Bacterial infections including bacteremia, pneumonia, sepsis, and meningitis, are rare concomitants of febrile seizures. None of the common childhood infectious illnesses, viral or bacterial, appears uniquely capable of activating febrile seizures.[9]

Methods:

This cross-sectional observational study was done with healthy Babies delivered and admitted to the inpatient postnatal ward of the department of pediatrics in Vydehi Institute of Medical Sciences And Research Center, Bangalore, during the study period (January 2015 – May 2016) Cases: Children aged 6 months-5years.Generalized tonic-clonic seizures occurring within 24hours of onset of fever. Seizures lasting for less than 15 minutes.A single episode of seizure per febrile illness. Without any post-ictal neurological deficit.Controls: Children with febrile illness without convulsions matched by age and sex, Exclusion criteria: Children with Iron supplementation/therapy, Hematological disorders

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Chronic illness Neurological deficit. After getting informed consent from the parents of cases and controls, they are subjected to a detailed history and clinical examination, and the findings are entered in the proforma. Blood samples are collected and measures of serum ferritin (the single most sensitive tool for evaluating the iron status) (21), Hemoglobin (HB), Mean corpuscular volume (MCV), and Mean corpuscular hemoglobin (MCH) are measured and compared. Serum ferritin estimation: Chemiluminescence immunoassay for the quantitative determination of serum ferritin. For this 2ml of blood was collected into vacutainers through venipuncture under strict aseptic precautions. The serum is separated from cells by centrifugation. The assay is based on microplates coated with highly specific anti-ferritin-human antibodies. During the procedure, the binding of the analyte, as well as the formation of the sandwich complex and enzymatic color reaction take place during three different reaction phases. Calibrators, controls, and undiluted patient samples are pipetted together with sample buffer into the wells of the microplate. Any present ferritin molecules bind to the inner surface of the wells. After 30 minutes of incubation, the microplate is washed with a buffer for removing non-reactive serum components. An anti-human-ferritin horseradish peroxidase conjugate solution is pipetted into the well of the microplate to recognize the ferritin bound to the immobilized antibody. After 15 minutes of incubation any excessive enzyme conjugate, which is not specifically bound is washed away with wash buffer. A chromogenic substrate solution containing TMB (3,3,5,5 tetramethyl-benzidine) was dispensed into the wells, during 15 minutes of incubation the color of the solution change to blue. Adding hydrochloric acid as a stop solution stops color development. The solution color changes to yellow. The amount of color is directly proportional to the concentration of ferritin present in the original sample. The optical density for each calibrator is graphically plotted against the concentration. Measurement of HB, MCV, and MCH is done by using an auto-analyzer (Coulter Counter)History elicitation, clinical examination, and investigations are carried out for cases and controls in a similar manner.

Statistical Analysis:

The effect of iron status on first febrile seizure with odds ratio (OR) and 95% confidence limit was arrived at by univariant analysis. An odds ratio was considered statistically valid and meaningful if the upper and lower limits of confidence interval do not include unity. The value of OR was considered significant if the probability (P) was <0.05. All continuous data were analyzed by the use of a t-test or Mann Whitney U test. All proportionate data were analyzed with chi-square or Fischer exact test.

Results :

Table: 1 Incidence Of Febrile Seizures Concerning Age And Gender.

Age	Male		Female		Total	
	N	%	N	%	N	%
6months-1year	7	11.1	5	8	12	19.1
1year-2year	20	31.7	17	27	37	58.7
2year-3year	10	15.9	4	6.3	14	22.2

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Total	37	58.7	26	41.3	63	100

TABLE :1 A maximum incidence of febrile seizures is found in the age group of 1year-2year (58.7%), followed by 2year-3year (22.2%) and 6months-1year(19.1%). The mean age is 18 months. The incidence of febrile seizures is found to be higher in males (58.7%) with a male: female ratio of 1.4:1. Eighteen children (28.5%) in the febrile seizures group have a positive family history of febrile seizures when compared to none among controls.

Table: 3mean Value Of Serum Ferritin And Blood Indices Among Those Who Had Febrile Seizures And Controls

S.No	Variables	Cases		Controls		P-value
		Mean	SD	Mean	SD	
1	Sr.Ferritin(ng/ml)	14.5	10.6	34.9	23.3	0.00
2	HB (gm%)	9.8	1.2	11.3	1.1	0.00
3	MCV (fl)	76.0	8.5	79.5	7.5	0.02
4	MCH (pg)	27.7	3.1	28.7	3.6	0.11

TABLE :3 The mean ferritin level among the febrile seizures group is found to be 14.5+/-10.6ng/ml whereas in controls it is 34.9+/-23.3ng/ml, (P=0.00). The mean Hemoglobin (HB) for cases is 9.8+/-1.2gm/dl, whereas in controls it is 11.3+/-1.1gm/dl (P=0.00). The Mean Corpuscular Volume (MCV) for cases is 76+/-8.5fl and for controls, it is 79.5+/-7.5fl, (P=0.02). The Mean Corpuscular Hemoglobin (MCH) for cases is 27.7+/-3.1pg and for controls it is 28.7+/-3.6pg (P= 0.11).Thus the mean serum ferritin, HB, and MCV are found to be signed on the lower side among children with febrile seizures when compared to the children who did not have febrile seizures, which is statistically significant. Even though the MCH is less among children with febrile seizures it did not achieve statistical significance.

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Table: 4 Proportion Of Children With Low Serum Ferritin/Blood Indices Among Cases And Controls

S.No	Variables		Cases		Controls		PValue
			N	%	N	%	
1	Serum ferritin (Ng/ml)	<10	41	65.1	15	23.8	0.00
		>/-10	22	34.9	48	76.2	
2	HB (Gm%)	<11	51	80.9	19	30.1	0.00
		>/-11	12	19.1	44	69.9	
3	MCV (Fl)	<70	23	36.5	8	12.7	0.003
		>/-70	40	63.5	55	87.3	
4	MCH (Pg)	<24	10	15.9	9	14.3	1.00
		>/-24	53	84.1	54	85.7	

TABLE:4 Forty-one children (65.1%) with febrile seizures have serum ferritin level <10ng/ml whereas only 15 children (23.8%) in the control group have ferritin level <10ng/ml with a (P=0.00).The number of children with hemoglobin <11gm/dl is 51 (80.9%) in the febrile seizures group whereas among controls it is only 19 (30%) (P=0.00).The Mean Corpuscular Volume <70fl is seen in 23 (36.5%) cases, whereas in controls it is only 8 (12.7%) (P= 0.003).*10 children (15.9%) in cases and 9 children (14.3%) in controls have Mean Corpuscular Hemoglobin <24pg (P=1).Thus a significant proportion of children with febrile seizures have low serum ferritin, Hemoglobin, and Mean Corpuscular Volume than did the controls. However, the proportion of children with low Mean Corpuscular Hemoglobin among those with febrile seizures and controls did not achieve statistical significance

Table: 5 Serum Ferritin And Blood Indices Among Cases And Controls:

S.No	Variables		Odds Ratio	95% CI	P-Value
	Serum ferritin	<10	6.0	2.7, 13.0	

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1	(ng/ml)	>/-10	1.0	Reference	0.00
2	HB (gm%)	<11	9.8	4.3, 22.5	
		>/-11	1.0	Reference	0.00
3	MCV (fl)	<70	4.0	1.6, 9.7	
		>/-70	1.0	Reference	0.003
4	MCH (pg)	<24	1.1	0.4, 3.0	
		>/-24	1.0	Reference	1.00

TABLE:5 Odds of children with febrile seizures having low serum ferritin levels is six when compared to those who did not have febrile seizures. OR (95%CI) = 6(2.7-13.0)Odds of children with febrile seizures having low Hemoglobin level is 9.8 when compared to those who did not have febrile seizures. OR (95%CI) = 9.8(4.3-22.5).Odds of children with febrile seizures having low Mean Corpuscular Volume is four when compared to those who did not have febrile seizures.OR (95%CI) = 4(1.6-9.7)*Odds of children with febrile seizures having low Mean Corpuscular Hemoglobin is1.1 when compared to those who did not have febrile seizures which is not statistically significant OR (95%CI) = 1.1(0.4-3)

Discussion:

Febrile Convulsions (FC) refer to the convulsions that occur in children between the ages of 6 months and five years, with a body temperature of 38ºC or higher not resulting from Central Nervous System (CNS) infection or any metabolic imbalance without any prior afebrile seizures. This condition occurs in 2-5% of the neurologically healthy children. The precise cause of FC is not known, but several genetic and environmental factors have been implicated. The maximum age of FC occurrence is 14-18 months, which overlaps with the maximum prevalence of Iron Deficiency Anemia (IDA) which is 1-2 years old. [10] IDA is the most common nutritional deficiency in the world. Iron is an important micronutrient that is used by roughly all the cells in the human body. It is well understood that iron is a cofactor for several enzymes in the body and has a role in neurotransmitter production and function, hormonal function, and DNA duplication.[11] In our study to detect low iron status as a possible risk factor for first febrile seizures, 63 cases, and 63 age and sex-matched controls are studied and analyzed. In the present study, we found that the peak incidence of febrile seizures occur between one to two years of age and the mean age is 18 months. [12] Hartfield D et al. reported no gender difference in their study. In our study family history of febrile seizures is seen only in 28.5% of cases. But Forfar textbook of pediatrics mentions that 50% will have a family history of convulsions and 80% of monozygotic twins are concordant for febrile convulsions.[13] The mean serum ferritin level in our study is 14.5ng/ml. whereas Kobrinsky NL et al. in his study group from Jordan found that the mean ferritin level was 29.5ng/ml [14] It is probably because iron deficiency anemia is more prevalent in our country; the mean serum ferritin level of Indian children is also low when compared to the Western standards. Livingston

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S. et al. in their study found that a significant proportion of children with febrile seizures had only low serum ferritin levels. The proportion of children with febrile seizures having low hemoglobin, Mean Corpuscular Volume and Mean Corpuscular. [15] Hemoglobin was not statistically significant. Whereas our study demonstrates a statistically significant difference in the proportion of children with febrile seizures who have not only low serum ferritin but also low hemoglobin and low Mean Corpuscular Volume. This is similar to the findings reported by Nelson KB et al. in their study at Karachi. This is probably because iron deficiency occurs in three stages. The first stage is characterized by decreased storage of iron without any other detectable abnormalities. An intermediate stage of `latent iron deficiency` i.e. iron stores are exhausted, but anemia has not occurred yet. The third stage is that of overt iron deficiency when there is a decrease in the concentration of circulating hemoglobin due to impaired hemoglobin synthesis.[16] As similar to previous studies by Pisacane A our study also demonstrates an association between iron deficiency and febrile seizures. Thus iron deficiency is one of the possible risk factors for febrile seizures. Developmental problems, risk of pediatric stroke, the occurrence of febrile seizures, and breath-holding spells are perhaps the tip of the iceberg, of the neurological consequences of iron deficiency.[17] With appropriate recognition, treatment, or better yet, prevention the neurological sequelae of iron deficiency are entirely preventable and perhaps reversible.[18]

Conclusion:

The peak incidence of febrile seizures is between one and two years of age. The mean Serum Ferritin, Hemoglobin and Mean Corpuscular Volume are significantly lower in children with febrile seizures as compared to controls. Significantly, a greater proportion of children with febrile seizures have low Serum Ferritin (<10ng/ml); low Hemoglobin (<11gm/dl), and low Mean Corpuscular Volume (<70fl) as compared to controls. Plasma ferritin levels and blood indices are significantly lower in children with febrile seizures as compared to children without febrile seizures suggesting that iron-deficient children are more prone to febrile seizures. A follow-up study of patients found to be iron deficient at the time of a first febrile seizure to determine the incidence of subsequent febrile seizures after treatment for iron deficiency would be of great interest.

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