



## Association between Iron Deficiency Anemia and Febrile Seizure: A Systematic Review and Meta-Analysis

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### ABSTRACT

Febrile seizure is the most common convulsive disorder in children and different studies reported controversial results about the association between this disorder and iron deficiency. In some studies, iron level in children with febrile seizure is higher than control and in some reports it is less than the control group. So, we systematically reviewed all the studies in this field and analyzed their findings using meta-analysis methods.

This review and meta-analysis was conducted by iron and fever keywords on articles published in the databases PubMed, Google Scholar and Federated search of medical digital library that includes a variety of international databases. All articles dated at the end of March 2012 were studied. Case-control studies were selected and quality assessment of studies were surveyed by STROB criteria and information requirements, including the status of iron deficiency anemia, iron levels and ferritin level of eligible studies were extracted and analyzed by Comprehensive Meta-Analysis Version 2.0 software and the Forest and Funnel chart was drawn.

Finally 11 studies included 1357 children with febrile seizure and 1347 children in the control group were evaluated. The odds ratio of iron deficiency anemia in children with febrile seizure in comparison to the control group was 1.27 (OR = 1.27, CI95%: 1.03 -1.56). Ferritin level was not significant between the two groups (p=0.08), but the iron level in the two groups was significant (p=0.000).

Iron deficiency is considered as a risk factor in the incidence of febrile seizure and interventional studies can be helpful to confirm this hypothesis.

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## Introduction

Febrile seizure is the most common neurologic disorder of children and the most frequent type of seizure in this age group. It occurs in 3%-4% of children under 5 years, most frequently from 14 to 18 months of age<sup>1, 2</sup>, although incidence rates as high as 14% have been reported.<sup>3, 4</sup> The recurrence rate of febrile seizure for the first time is 50% in children under 1 year of age and 28% for those older than 1.<sup>5</sup> The simple febrile seizures are diffuse seizures lasting less than 15 minutes and occurring only once over 14 hours. If focal seizure or focal symptoms following the seizure are multiple or lasting more than 15 minutes, the seizure will be termed complex febrile seizure.<sup>6</sup> Febrile seizure is more common in boys, usually manifesting as tonic-clonic convulsion.<sup>7</sup> Simple febrile seizure reflects a genetic predisposition to convulsion manifesting with abrupt elevation of body temperature.<sup>8</sup> Otitis media, roseola, and upper respiratory tract infections (especially influenza) are among the most common clinical conditions resulting in febrile seizure in children.<sup>9</sup> The pathophysiology of febrile seizure remains to be accurately described<sup>10</sup>; different studies have reported various risk factors, including iron deficiency.<sup>11, 12</sup> On the other hand, there are studies that fail to corroborate such an association, as well as those which demonstrate the opposite.<sup>13, 14</sup> Therefore, since iron deficiency anemia is a common disorder of pediatrics and preliminary data have failed to demonstrate a definitive association, we undertook the present study to investigate the association between iron deficiency anemia and febrile seizure in children.

## Methods

This is a review and meta-analysis on studies addressing the relationship between febrile seizure in children and iron level.

**Search Strategy:** We completed a search in databases such as PubMed, and Google Scholar as well as the digital medical library consisting of BMJ Journals, CINAHL, Cochrane Library, ProQuest, Science Direct, Scopus, Oxford Journals, Wiley and Web of Science dated at the end of March 2012. In PubMed, we searched for the key term “febrile” in [Title] and “Iron” in [All Fields], limiting the results to the age group under 18. The search in Google Scholar was accomplished by searching for key terms “febrile” and “iron” in [Title]. As for the digital medical library, we searched for the key term “febrile” in [Title] and “iron” in [Full Text].

**Inclusion criteria:** All case-control studies conducted on children were included in the study without any language limitations. Other types of research, particularly letters to editor, were eliminated. We selected those studies in which at least one of the variables of iron level, ferritin level, or iron deficiency anemia rate was reported or calculable.

**Study Selection:** All selected articles were evaluated by two individuals independently and in a blinded fashion. The evaluation was first performed on the abstracts and then the full texts. Any disagreement among the reviewers would be resolved through discussions.

**Study Quality Control:** The quality of studies was assessed using the Strobe criteria. Among the final articles approved, there was only one article written in a language other than English. It was translated into English using Google Translator; as the main data of the study were presented in tables in English, we were able to include it in the final analysis with confidence.

**Data Extraction:** The required information was extracted by two individuals independently and in a blinded fashion. The information was recorded on particularly designed sheets. Any disagreement between reviewers would be

**Table 1.** Studies included in the review

Author	Number		Iron Level (Mean ± Standard Deviation)			Iron Deficiency Anemia Rate (%)			Ferritin Level (Mean ± Standard Deviation)		
	Case	Control	Case	Control	P Value	Case	Control	P Value	Case	Control	P Value
Daod <sup>11</sup>	75	75	-	-	-	65	32	0.000	29.5 ± 21.3	53.3 ± 37.6	0.001
Kumari <sup>12</sup>	154	154	-	-	-	63.6	24.7	0.001	-	-	-
Abbaskhanian <sup>13</sup>	100	100	73.4 ± 31.8	49.8 ± 15.7	0.006	42	60	0.016	89.2 ± 49.13	76.9 ± 28.8	0.032
Hartfield <sup>14</sup>	361	390	-	-	-	6	4	0.29	-	-	-
Amirsalari <sup>15</sup>	132	88	-	-	-	26.5	29.5	0.623	-	-	-
Vaswani <sup>16</sup>	50	50	-	-	-	-	-	-	31.9 ± 31	53.9 ± 50.5	0.003
Bidabadi <sup>17</sup>	200	200	58.5 ± 35.3	49.7 ± 22.3	0.003	44	48	0.483	100.2 ± 114.2	75.2 ± 50.8	0.005
Salehiomran <sup>18</sup>	90	90	-	-	-	-	-	-	73.5 ± 67.1	82.1 ± 91.3	0.474
Momen <sup>19</sup>	50	50	-	-	-	-	-	-	30.3 ± 16.5	84.3 ± 28.5	0.000
Im <sup>20</sup>	45	50	-	-	-	-	-	-	27.5 ± 20.2	22.5 ± 15.6	0.17
Jun <sup>21</sup>	100	100	-	-	-	39	28	0.134	-	-	-

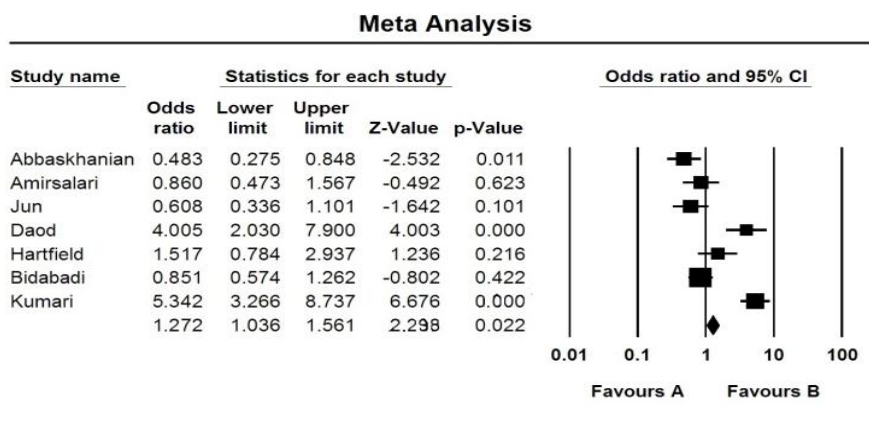
settled through discussions. The data sheet included: general information of the study (title and authors), sample size in each group, iron level, ferritin level, and iron deficiency anemia rate in both groups.

**Data Analysis:** Data were analysed on Comprehensive Meta-Analysis Software the Version 2.0. Forest diagrams were plotted for three main indices, and Funnel diagram was drawn for two indices of iron deficiency anemia rate and ferritin level to indicate lack of publication bias (as iron level was mentioned in only two studies).

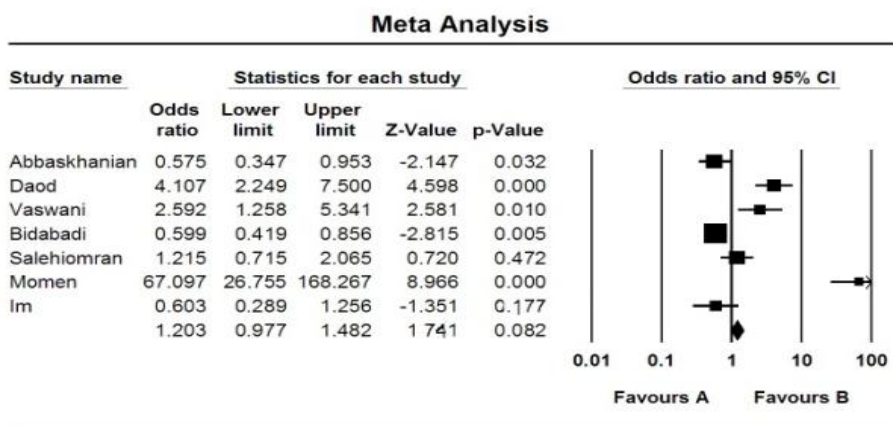
## Results

Eventually, 11 studies comprising 1,283 children with febrile seizure and 1,272 children in control groups were reviewed. Out of the 11 studies, 7 reported ferritin levels, 2 reported iron deficiency anemia rate, and 2 reported iron levels (table 1).

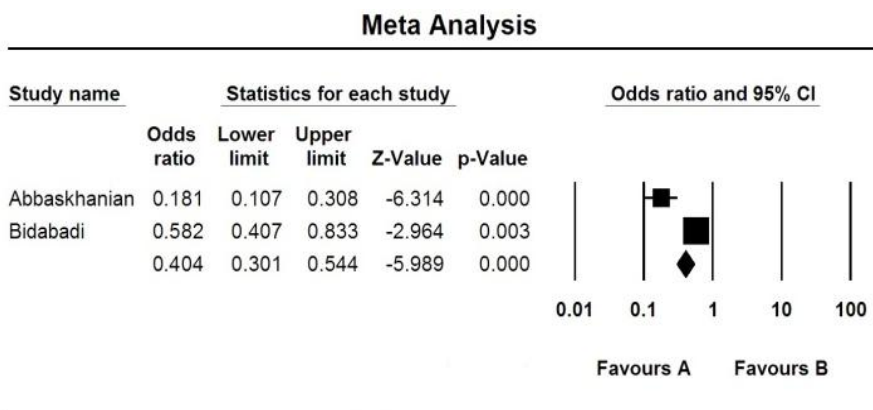
Figure 1 depicts the accumulation diagram (Forest plot) of iron deficiency anemia in children with febrile seizure. The odds ratio of iron deficiency anemia in children with febrile seizure is 1.27 times greater than the control group (OR = 1.27; CI95%: 1.03 – 1.56). Figure 2 presents the accumulation diagram of ferritin



**Figure 1.** Forest plot of association between iron deficiency anemia and febrile seizure



**Figure 2.** Forest plot of association between ferritin level and febrile seizure



**Figure 3.** Forest plot of association between iron level and febrile seizure

level in both groups, indicating lack of significant relationship between ferritin levels in the two groups ( $p=0.08$ ), although ferritin levels were lower in children with febrile seizure.

Figure 3 depicts accumulation of iron level in both groups, with children with febrile seizure having significantly higher iron levels ( $p=0.000$ ).

## Discussion

Numerous studies have addressed the association between iron deficiency anemia and febrile seizure in children both in Iran and abroad. The results, however, have been controversial and even primary researches with high number of cases have failed to provide unequivocal results. The systematic review and meta-analysis of the results indicated that iron deficiency may constitute a risk factor for febrile seizure. Iron is an essential element for metabolism, with many enzymes depending on its function. Iron is involved in metabolism of neurotransmitters and enzymes such as monoaminoxidase, cytochrome, peroxidase, and catalase. It is well established that iron deficiency may cause behavioral and developmental disorders.<sup>11</sup> This association confirms the hypothesis that the dysfunction of neurotransmitters caused by iron deficiency may render the child susceptible to febrile seizure.<sup>14</sup>

Despite the number of original studies on this subject, no systematic review and meta-analysis has been conducted so far; only one case-control study on children with febrile seizure has conducted a meta-analysis on several case-control studies, yielding results consistent with our findings – i.e. iron deficiency is a risk factor for acute seizure in children.<sup>22</sup> Ferritin level denotes body supplies of iron<sup>19</sup> and our meta-analysis indicates that ferritin levels in children

with febrile seizure are lower compared to the control group; the difference, however, was not statistically significant.

## Conclusion

In conclusion, it may be stated that iron deficiency is a risk factor for febrile seizure and interventional studies may be designed to verify this hypothesis.

## Conflict of Interest

None declared.

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