ORIGINAL ARTICLE

Serum and Cerebrospinal Fluid Lactate Dehydrogenase in Children with Febrile Convulsions

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Abstract

Objective

Tissue damage caused by febrile convulsion has not still been proved or refuted completely. Given the fact that lactate dehydrogenase as an intracellular enzyme can be increased due to tissue damage, we decided to evaluate serum and cerebrospinal fluid lactate dehydrogenase in children with febrile convulsion.

Materials & Methods

This is a cross-sectional study on 166 children aged 6-24 month, in three groups of simple febrile convulsion (n=56), complex febrile convulsion (n=27) with 3 different subgroups (recurrence in 24 hours, duration >15 minutes, and with focal components), and control (n=83). Patients' serum and cerebrospinal fluid specimens were collected after meeting the inclusion criteria. Demographic information was documented and patients' serum and cerebrospinal fluid lactate dehydrogenase and glucose were measured. Data were analyzed using SPSS software.

Result

The mean serum lactate dehydrogenase in simple febrile convulsion, complex febrile convulsion, and controls were 501.57± 143.70, 553.07±160.22, and 505.87±98.73 U/L, respectively. The mean cerebrospinal fluid lactate dehydrogenase in simple, complex febrile convulsion, and control groups were 22.58±11.92, 29.48±18.18, and 21.56±17.32 U/L, respectively. Only cerebrospinal fluid lactate dehydrogenase difference between complex febrile convulsion and control group (p=0.039) (In the duration >15 minutes subgroup and controls, p=0.028) was statistically significant. There was a significant

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difference between sex and serum lactate dehydrogenase in the same subgroup of complex group (p=0.012).

Conclusion

Complex febrile convulsion may lead to increase of lactate dehydrogenase in cns of CNS cellular damage.

Keywords: Cerebrospinal Fluid; Lactate Dehydrogenase; Convulsions; Febrile; Seizure, Febrile; Complex; Pediatrics
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Introduction

Febrile convulsion (FC) is one of the most stressful clinical conditions that affects children aged 6 to 60 months, irrespective of sex, and it occurs in tandem with a fever with a body temperature of 38°C or higher. The fever in these patients is not caused by intracranial issues (e.g. head trauma and infection) or other remarkable conditions (e.g. electrolyte imbalance, drug use, or withdrawal, and hypoglycemia) and patients do not have any history of previous afebrile seizures (1-4). FC is divided into two categories: simple and complex. The febrile stage is a prerequisite condition in both categories. Febrile episodes are very common experiences that occur in the first year of every children's life, but only 2 to 5 percent of them are suffering from FC. The etiology is unknown, however, certain features such as genetic factors with specified chromosomes could also be possible candidates.

Prolonged FC may lead to many devastating clinical consequences. Acute hippocampal injury, increased risk of epilepsy, and mesial temporal sclerosis are the proven aftereffects of prolonged febrile seizure (5). Crespel et al. demonstrated that recurrent seizures play the main role in inflammatory processes, in epileptic hippocampi with typical sclerosis (6). Theodore et al. suggested that persistent seizures may lead to progressive hippocampal formation damage in patients with complex partial seizures (7). Also, Cendes et al. demonstrated that a history of prolonged febrile convulsions in early childhood may affect the atrophy of mesial structures and mesial temporal sclerosis (8). Therefore, there is debate about whether simple and complex FC may lead to some degrees of tissue damage and alteration in aerobic and anaerobic metabolisms.

Lactate dehydrogenase (LDH) is a ubiquitous intracellular enzyme found in many body tissues and fluids such as cerebrospinal fluid (CSF). LDH is essential for energy metabolism of neuronal cells; lactate can be used as a main energy source for neurons in the conditions such as seizures, that brain tissue requires high energy consumption (9). Consequently, any clinical conditions which cause tissue damage, such as hemolysis, cancer, severe sepsis, infections, muscle injuries, brain infarct, liver diseases, and many others may lead to increased serum LDH (10,11). Additionally, elevated CSF LDH in infantile spasm, hydrocephalus, bacterial meningitis, cerebral malignancy, cerebrovascular accidents, Guillain-Barre syndrome, and Creutzfeldt-Jakob have previously been reported.

Therefore, serum and CSF LDH levels can be used to determine the damage caused by aerobic or anaerobic metabolisms during fever, and thereupon may help to reveal patients' prognosis (12-16). But increased serum and CSF LDH levels in FC have not yet been proven and there are a few published studies of serum and CSF LDH in febrile convulsions, and their results remain unclear. The purpose of the present study was to determine of serum and cerebrospinal fluid LDH in children with simple and complex febrile convulsions and their comparison with each other and controls.

Materials & Methods

This is a cross-sectional study conducted on all normal growth children aged 6 to 24 months, hospitalized because of simple or complex FC in the Rasht 17 Shahrivar Hospital. Simple FC referred to convulsions which are generalized, last less than 15 minutes, and do not occur more than once during 24 hours, whereas complex febrile seizures have the following characteristics: duration more than 15 minutes and/or focal component and/or recurrence during 24 hours (2,17). The control group consisted of the same age children admitted in the hospital because of fever, without recent or previous history of convulsions. All three simple FC, complex FC, and control groups were matched in terms of age and sex and enrolled after obtaining informed consent from their parents. Demographic data such as age, sex, and type of convulsion (simple or complex) of all subjects were documented.

Based on the recommendation of the American Academy of Pediatrics (AAP), that lumbar puncture (LP) be strongly considered for children with less than 12 months, and be considered for children with 12-18 months of age, for diagnosis of bacterial meningitis among patients with first simple febrile convulsion (18); and recommendation of the Royal College of Physicians and the British Paediatric Association Joint Working Group (19) about performing LP in patients with meningism, complex febrile convulsions, drowsy or irritable, and probably in children with age of <18 months and definitely in <12 months, we enrolled only the 6 months to 2 years old patients with febrile convulsions in this study.

All three simple FC, complex FC, and control group were matched in terms of age and sex ratio. Informed consent was obtained from all parents. Demographic data such as age, sex, and type of convulsion (simple or complex) of all subjects were documented.

Lumbar puncture and neuroimaging were performed for all patients and they were excluded from the study if they had bacterial meningitis, aseptic meningitis, neurological disease, dehydration, traumatized LP, hydrocephalus, brain tumor, and status convulsion (20).

The study was under the Helsinki Declaration. Before the study started, the purpose of the study was explained to all parents and informed consent for participation in the study was obtained from the parents or legal guardians of minors. Eventually, the study was approved by the Institutions' Ethical Committee of Guilan University of Medical Sciences.

Sample collection:

A half cubic centimeter of serum and CSF of the patients were collected in the first 12 hours of hospitalization. LDH and glucose of both samples were evaluated. Only specimens remained enrolled that their smears and CSF cultures were negative, LP findings (WBC, RBC, protein, and glucose) were normal and did not have meningitis or sepsis (positive blood cultures).

Serum and CSF samples were collected in sterile and metal-free laboratory tubes and stored at -4°C in the hospital laboratory for later analyses. CSF was analyzed using the BT-2000 autoanalyzer produced by the Biotechnica Instruments industry. Pars-Azmun kits were used to measure glucose and LDH in serum and CSF, and Ziest-Chem kits were used to measure CSF protein.

Statistical analysis:

All data were analyzed using SPSS 19 software. The Kolmogorov-Smirnov test was used for estimation of distribution of quantitative variables. Non-parametric tests were used since the data did not have a normal distribution. Consequently, the Mann-Whitney test was used to compare serum and CSF LDH levels and the t-test was used to compare the age frequency. Chi-square test was used to determine the sex frequency. Also, the one-way ANOVA test was used to evaluate the correlation between age and sex with serum and CSF LDH levels in simple and complex FC groups. Significance of p-values were considered less than 0.05.

Results

Of 166 patients recruited in this study, 56 patients had simple FC, 27 patients had complex FC (18 with recurrence during 24 hours, 5 with duration >15 minutes, and 4 with focal component), and 83 patients were hospitalized for causes other than FC (controls). All patients aged 6 to 24 months old. The baseline characteristics of the patients and the total serum and CSF LDH levels in each specific group and subgroups are shown in Table 1. There was no significant difference between age and sex of groups.

According to the Mann-Whitney test, for pairwise comparisons as a post hoc analysis, serum and CSF LDH levels had no significant difference between the simple FC and control groups (p=0.712 and 0.163, respectively). Although serum LDH levels between the complex FC and control group had no significant difference (p=0.749), the CSF LDH level difference between these two groups was statistically significant (p=0.039) (p=0.083 and 0.028 and 0.165, for recurrent and >15 minutes and focal subgroups, respectively). Serum and CSF LDH levels had also no significant difference between the simple FC and complex FC groups (p=0.469 and 0.118, respectively).

No significant correlation between age and sex with serum and CSF LDH levels in both groups of simple and complex FC were found according to the one-way ANOVA test, except for sex and serum LDH level in duration of >15 minutes subgroup of complex FC (p=0.012). Table 2 shows mean serum and CSF LDH levels in simple and complex FC according to age and sex, respectively.

Table 1. Baseline characteristics, total serum and CSF LDH level in simple FC, complex FC and control groups.

		Simple FC (n=56)	Complex FC (n=27)	Control (n=83)	P-value
Age in month (mean ± SD)		12.79 ± 5.12	14.22 ± 4.30	12.65 ± 4.27	0.287
Sex, No. (%)					
Girl	Boy	33 (58.9%)	15 (55.6%)	43 (51.8%)	0.708
	23 (41.1%)	12 (44.4%)	40 (48.2%)		
LDH level (U/L) *					
Serum		501.57±143.70	553.07±160.22	505.87±98.73	-
CSF		22.58±11.92	29.48±18.18	21.56±17.32	-

CSF, cerebrospinal fluid; LDH, lactate dehydrogenase; FC, febrile convulsion; SD, standard deviation; U/L, unit per liter
* In comparison of serum and CSF LDH levels between the groups, only the difference between CSF LDH level of complex FC and controls was significant (p=0.039).

Table 2. Serum and CSF LDH levels in simple and complex FC according to age and sex.

	Simple FC		Complex FC	
	Serum LDH (mean ± SD)	**CSF LDH (mean ± SD)**	**Serum LDH (mean ± SD)**	**CSF LDH (mean ± SD)**
Age				
6-10 months	545.65±170.65	21.20±13.79	543.83±137.74	39.66±17.25
11-15 months	466.21±157.85	23.26±11.75	569.90±178.01	26.36±17.97
16-20 months	475.36±77.49	26.54±9.28	540.10±166.79	26.80±18.48
21-24 months	514. 66±23.03	17.83±9.94	---	---
Total	501.57±143.70	22.58±11.93	553.07±160.22	29.48±18.18
Sex				
Male	503.94±154.62	24.45±13.00	503.30±144.54	26.23±20.34
Female	497.61±126.96	19.47±9.33	574.21±176.22	32.50±16.08

CSF, cerebrospinal fluid; LDH, lactate dehydrogenase; FC, febrile convulsion; SD, standard deviation

Discussion

FCs are defined as age-specific convulsions occur following a febrile episode of 38.0°C or higher in children aged 6 to 60 months in the lack of any intracranial issues (such as infection, brain tumor or head trauma), metabolic disturbance, hypoglycemia, or a history of previous afebrile seizure, which are divided into two subcategories of simple and complex (4). Unfortunately, FC is an intimidating clinical condition that has a psychological burden for patients' parents and the fear of persistent brain injury and developmental disorders always exist (21).

LDH is an omnipresent zymotic enzyme found

in body tissues and fluids such as CSF which is increased following tissue damage. Nowadays, CSF LDH levels are of paramount importance in diagnosing many intracranial issues such as infections, brain tumors, hydrocephalus, and raised intracranial pressure (22).

Lending et al. in 1964 indicated that the upper limit of normal for CSF LDH is 40 U/L (23). Thereafter, an increased level of CSF LDH in intracranial infections, infantile spasm, hydrocephalus, strokes, Guillen Barre syndrome, and Creutzfeldt-Jakob disease was demonstrated in different studies (24-29).

Although Nelson et al. revealed an increase in the level of CSF LDH in the meningitis (especially bacterial meningitis), CNS leukemia, epileptic seizures, increased intracranial pressure, and hydrocephalus, but no significant increase in the CSF LDH level of children with FC was reported with them (22). Our results showed an increase in CSF LDH levels of patients with complex FC in comparison with other groups, however, only the difference between complex FC and control group was significant. Although serum LDH levels in patients with complex FC were more than other groups, the results were not statistically significant, which may be due to the small sample size. Also, there was no significant correlation between age and sex with serum and CSF LDH levels in our study, except for sex and serum LDH level in duration of >15 minutes subgroup of complex FC.

Ehsanipour et al. in a cross-sectional study on 225 children noted that simple and complex FC may lead to tissue damage and alteration in aerobic and anaerobic metabolism. CSF LDH level increased more in complex FC group than simple FC in their study (15). These results were almost in line with our study. In another study by Nussinovitch et al. (12) it was noted that focal and general FCs do not lead to tissue damage and alteration in aerobic and anaerobic metabolism, as CSF LDH levels remained intact, which are in contrast with our results. Possible explanations for these discrepancies are small sample size and disparity between the case and control groups in terms of number (31 vs. 84).

Our study had some inevitable limitations such as a small sample size, especially in the complex FC subgroups, and lack of access to laboratory kits for evaluating LDH isoenzymes. A larger sample size of subjects may affect the accuracy of the results.

As demonstrated in our study, it can be concluded that complex FC may lead to some degree of CNS cellular damage.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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