

Lactic dehydrogenase isoenzymes in cerebrospinal fluid of children with Guillain–Barré syndrome

M Nussinovitch, D Prais, Y Finkelstein, D Harel, J Amir, B Volovitz

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See end of article for authors' affiliations

Correspondence to:
Dr M Nussinovitch,
Department of Pediatrics
"C", Schneider Children's
Medical Center of Israel,
Petach Tikvah, Israel;
moshen@post.tau.ac.il

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Background: Increased levels of lactic dehydrogenase (LDH) in the cerebrospinal fluid (CSF) have been reported in association with several intracranial pathologies. No studies have been performed on patients with Guillain–Barré syndrome (GBS).

Aims: To study LDH isoenzymes in CSF of children with GBS.

Methods: CSF samples collected from nine patients with GBS were analysed for total LDH isoenzymes activity, and compared to samples from 15 patients with normal results.

Results: Mean total LDH activity was 33.33 (6.63) U/l. All patients had significantly increased LDH-3 isoenzyme compared to controls. LDH-3 was the predominant fraction, accounting for more than 50% of total LDH activity and present in more than twice the percentage of LDH-1 or LDH-2. By contrast, in the control group, there were high percentages of mainly LDH-1 and LDH-2.

Conclusions: GBS is apparently associated with a distinct LDH isoenzyme pattern in the CSF. More studies are needed to confirm the rise in LDH-3, as serial CSF analyses are unavailable, and to determine the optimum time of analysis when this finding first becomes detectable.

Lactic dehydrogenase (LDH) is present in most tissues and body fluids examined, including cerebrospinal fluid (CSF). Studies have shown that patients with an intracranial pathology such as malignancy or bacterial infection have increased CSF LDH activity compared to healthy subjects (normal 40 U/ml).^{1–3}

To the best of our knowledge, no reports have been published regarding CSF LDH activity in Guillain–Barré syndrome. In the present study we present nine children with a diagnosis of Guillain–Barré syndrome in whom the CSF showed a distinctive LDH isoenzyme pattern.

SUBJECTS AND METHODS

The study sample consisted of nine patients, aged 15 months to 9 years, with suspected Guillain–Barré syndrome, who underwent routine lumbar puncture at an inpatient department of our tertiary paediatric centre. The authors of this study did not participate in the clinical management of these patients. CSF analyses included total and differential cell counts, glucose and protein concentration, and cultures. None of the samples was bloody. One ml of CSF was stored at –20°C for later analysis of total LDH activity and LDH isoenzymes.

All patients fulfilled the clinical and laboratory diagnostic criteria for Guillain–Barré syndrome according to Asbury.⁴ Therefore, an increased protein concentration was required for diagnosis. The CSF LDH findings in the study patients were compared with those in 15 patients of mean age 10 (6.4) months who had undergone lumbar puncture during the same period because of suspected intracranial pathology with normal CSF findings. No relation between serum and spinal fluid activity has been noted; each varies independently of the other, presumably because of the blood–brain barrier.

Total LDH activity in the CSF samples was measured on a Hitachi-747 analyser (Boehringer-Mannheim) with an LDH kit (Boehringer-Mannheim) using the optimised standard methods. The LDH activity of spinal fluid appears to bear no direct relation to initial pressure, erythrocyte count, protein, and sugar.¹

RESULTS

Table 1 summarises the epidemiological and laboratory data of the patients. Besides the lumbar puncture, the laboratory results

were within normal limits; serology and culture studies were negative for *Campylobacter jejuni*. In all nine patients, the CSF protein concentration was high (92–252 mg/dl) without pleocytosis (<6 WBC/mm³). Electromyography, performed in three of the nine patients, revealed evidence of acute denervation of muscle, with or without fibrillation.

Mean LDH activity in the CSF was 33.33 (6.63) U/l. In none of the patients was a value higher than 45 units detected, indicating that in all cases, total CSF LDH activity was within the normal range.

Table 2 presents the distribution of CSF LDH isoenzymes in the patients. This pattern is also illustrated in fig 1B. The same data for the control group are presented in table 2 and fig 1A. It is noteworthy that the control group samples showed elevations in LDH-1 and LDH-2 ($p < 0.01$) percentages and LDH-3 to a lesser extent. Only low percentages of LDH-4 and trace levels of LDH-5 were noted. By contrast, all patients with Guillain–Barré syndrome had notable increases of LDH-3 ($p < 0.01$). The LDH-3 isoenzyme was the predominant fraction, accounting for more than 50% of the total LDH activity and was present in more than twice the percentages of either LDH-1 or LDH-2.

DISCUSSION

To the best of our knowledge, this is the first report on the LDH isoenzyme pattern in the cerebrospinal fluid of patients with Guillain–Barré syndrome. In typical cases of Guillain–Barré syndrome, diagnosis is not difficult, though laboratory studies are often not helpful in the early stages of the disease. Prototypical laboratory results include albuminocytological dissociation in the CSF, and evidence of slowed nerve conduction on electrodiagnostic studies. However, the CSF protein level may not rise until a week after onset of symptoms, and the characteristic electrodiagnostic findings may not be evident until well after the clinical features are established.⁴ In these atypical

Abbreviations: CSF, cerebrospinal fluid; GBS, Guillain–Barré syndrome; LDH, lactic dehydrogenase

Table 1 Summary of cases of Guillain-Barré syndrome

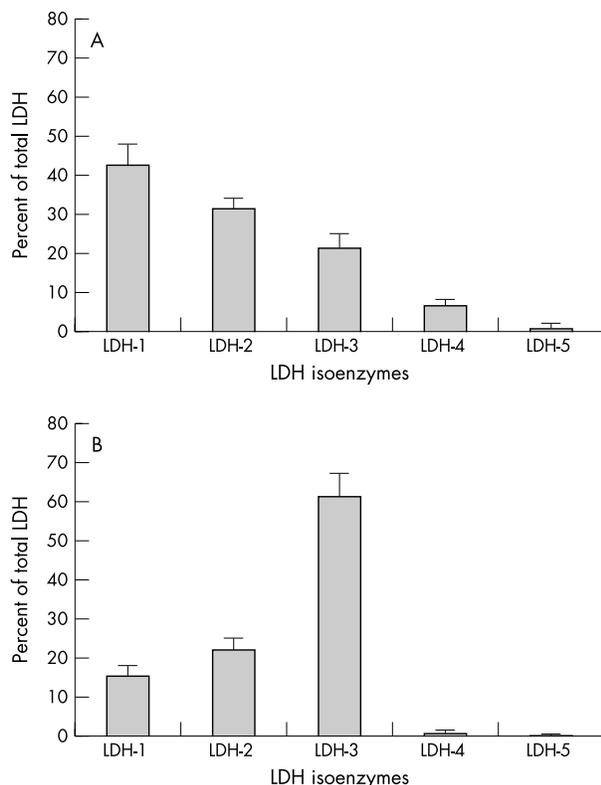
Case	Age (y)	Sex	CSF protein (mg/dl)	CSF WBC/mm ³	Cultures	Antecedent condition	LP day
1	9	Male	252	0	Neg		9
2	1.4	Female	130	1	Neg	URI	8
3	4	Male	128	5	Neg		8
4	4.5	Male	145	0	Neg		7
5	3.4	Male	92	0	Neg	URI	6
6	7.5	Female	98	5	Neg		7
7	2.5	Male	158	0	Neg		7
8	1.4	Female	220	0	Neg	URI	12
9	5	Female	182	6	Neg		9

CSF, cerebrospinal fluid; LP, lumbar puncture; Neg, negative; WBC, white blood cell count; URI, upper respiratory infection.

Table 2 LDH in CSF of patients with Guillain-Barré syndrome versus normal controls

	Normal controls (n=15)	Guillain-Barré syndrome (n=9)
Total LDH (U/l)	33.53 (5.75)	33.33 (6.63)
LDH-1 (%)	42.19 (5.44)	15.34 (2.97)*
LDH-2 (%)	30.96 (2.58)	22.02 (2.94)*
LDH-3 (%)	20.64 (3.69)	62.14 (5.53)*
LDH-4 (%)	6.20 (1.74)	0.48 (0.97)
LDH-5 (%)	0 (0)	0 (0)

All values are mean (SD).
*p<0.01.

**Figure 1** Percentage of total LDH in CSF of patients with Guillain-Barré syndrome (B) versus normal patterns (A).

cases, the analysis of LDH isoenzyme in CSF may serve as a useful, auxiliary tool for diagnosis. It is rapid, simple, and easily available, considering that all patients with suspected Guillain-Barré syndrome undergo lumbar puncture.

The most important finding of this study is the distinct pattern of isoenzyme distribution in Guillain-Barré syndrome in

the presence of normal total CSF LDH activity. A comparison of figs 1A and B emphasises the clinical value of this finding. A predominance of LDH-3 activity, namely more than 50% of normal and/or twice that of either LDH-1 or LDH-2 accompanied by an acute progressive polyneuropathy is almost diagnostic of Guillain-Barré syndrome. The specificity of this finding in other clinical settings remains unclear.

Several conditions are known to modify the normal CSF LDH isoenzyme distribution, including bacterial meningitis (increase in LDH-4 and LDH-5), viral meningitis (increase in LDH-1 and LDH-2), intracranial tumours (LDH-5), cerebral haemorrhage (LDH-3, LDH-4, and LDH-5), leukaemic and lymphomatous infiltration (LDH-3 and LDH-4), and tuberculous meningitis (LDH-3).^{5,6}

The origin of the increased LDH in the CSF of patients with a pathology of the central nervous system is not understood. Some authors have suggested a disturbance in the brain barrier which permits plasma LDH to reach the CSF, or LDH production by neoplastic tissue or white blood cells and exogenous bacterial sources.^{1,2,5,6} However, neither of these has yet been proven. The spinal fluid level varies independently of the plasma or serum activity.¹

The present study suggests that LDH isoenzyme analysis may contribute to the diagnosis of the syndrome. More studies are needed to confirm the rise in LDH-3, as serial CSF analyses are unavailable, and to determine the optimum time of analysis when this finding first becomes detectable.

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Authors' affiliations

M Nussinovitch, D Prais, Y Finkelstein, Jacob Amir, B Volovitz, Department of Pediatrics "C", Schneider Children's Medical Center of Israel, Sackler School of Medicine, Tel Aviv University, Petach Tikvah, Israel

D Harel, Laboratory of Clinical Chemistry, Rabin Medical Center, Beilinson Campus, Sackler School of Medicine, Tel Aviv University

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IMAGES IN PAEDIATRICS.....

Respiratory failure due to pulmonary calcification in primary hyperparathyroidism

A 5½ year old boy presented with fever, limb pain, polydipsia, and polyuria for 18 months, and respiratory distress for two weeks. His weight and length were below the 5th centile and he had multiple enlarged lymph nodes and hepatosplenomegaly. He was tachypnoeic with retractions, and had bilateral scattered crepitations. A chest x ray showed a dense homogeneous opacity on the left and right hilar prominence, with healed rib fractures. There was cupping and fraying at the ends of long bones, with osteopenia and pencil thinning of cortex. Serum calcium was 2.6 mmol/l, phosphorus 1.48 mmol/l, and alkaline phosphatase 3790 U/l. A presumptive diagnosis of disseminated tuberculosis, rickets, and scurvy was made and he was started on appropriate therapy.

Within a month, he presented with a pathological fracture in the left tibia and worsening respiratory distress. He was emaciated, oxygen dependent, and hypertensive (BP 130/110 mm Hg). Serum calcium was 3.3 mmol/l and phosphorus 0.77 mmol/l. Figure 1 shows chest x ray; limb x rays showed osteopenia, bone resorption, and calcification of the radial artery. Ultrasound of the neck showed right parathyroid adenoma (fig 2); serum intact parathormone level was 122.7 pmol/l. A 3×3 cm parathyroid adenoma was excised surgically and comprised of clear and chief cells. Postoperatively, he required ventilatory support for 40 days. Radiologically, his lung shadows initially worsened and then partially cleared. He has been on follow up for a year and has remained normocalcaemic. Chest x ray shows partial clearing (fig 3).

Primary hyperparathyroidism is rare in children.¹ Solitary adenomas account for the majority of such cases.² Metastatic calcification is rare in primary hyperparathyroidism.³⁻⁵ With lung involvement, the x rays have often been interpreted as pneumonia, interstitial fibrosis, or atelectasis.³⁻⁵ Metastatic calcification of the lung has not been reported in children.

B Poddar, S Bharti, V R Parmar

Department of Pediatrics, Government Medical College and Hospital, Chandigarh, India

R Sidhu

Department of Radiodiagnosis, Government Medical College and Hospital, Chandigarh

S Chowdhary, K L N Rao

Department of Pediatric Surgery, Post Graduate Institute of Medical Education and Research, Chandigarh, India
Correspondence to: Dr B Poddar, Reader, Department of Pediatrics, Govt Medical College and Hospital, Sector 32, Chandigarh – 160 030, India; bananip@hotmail.com



Figure 1 Initial x ray.

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Figure 2 Neck ultrasound, showing right parathyroid adenoma.



Figure 3 Postoperative x ray.