SHORT REPORT

LDH isoenzymes in cerebrospinal fluid in various brain tumours

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Abstract

This study examined the isoenzymatic pattern of LDH in the cerebrospinal fluid (CSF) as well as the ratio between the five fractions of LDH among patients with various brain tumours, carcinomatous meningitis and control groups. LDH 1/LDH 2 <1 was found significant for carcinomatous meningitis ($p < 0.001$) and brain metastases ($p < 0.001$). LDH 1/LDH 2 ratio was found to be significantly lower in carcinomatous meningitis than in brain metastases ($p < 0.05$). No LDH 1/LDH 2 ratios smaller than 1 were found in the other groups. The LDH 1/LDH 2 ratio smaller than 1 was found in the early stage of carcinomatous meningitis without other evidences of the involvement of the leptomeninges. Examination of LDH 1/LDH 2 can be found as an adjunctive method to identify brain metastases and carcinomatous meningitis at the initial stage.

The isoenzymatic distribution of lactate dehydrogenase (LDH) in patients with brain tumours was previously examined in serum,¹⁻⁹ brain tissue,⁴⁻⁹ and cerebrospinal fluid (CSF).^{1,3,8} Few studies demonstrated an elevation of LDH 5 fraction and decrease in the ratio of the LDH subunit monomers A to B^{7,9,10} in patients with malignant brain tumours. In patients with benign intracranial tumours, an increase of the LDH 1 fraction was observed. Studies which examined the LDH isoenzymatic pattern in CSF of patients with systemic cancer have already been published.¹¹ No observations of changes in the ratio LDH 1 to LDH 2 have been published to date. Due to the absence of an early objective laboratory measure to identify intracranial malignancy, we examined the LDH isoenzymatic pattern in various brain tumours and carcinomatous meningitis. The ratios between the single LDH fraction were calculated.

Patients and methods

The LDH levels and the isoenzymatic distribution were examined in the serum and CSF of 58 patients with primary benign tumours ($n = 12$), primary malignant

tumours ($n = 15$), cerebral intraparenchymatous metastases ($n = 21$), and pulmonary carcinomatous meningitis ($n = 4$). The following control groups were examined: 80 patients with epilepsy and cerebral degenerative diseases ($n = 20$), stroke ($n = 20$), viral meningitis and meningioencephalitis ($n = 20$), and patients with intervertebral disc herniation ($n = 20$). Among the primary brain tumours, 10 meningiomas, one dermoid and one haemangioblastoma were diagnosed. Among the primary malignant tumours, 14 were gliomas and one oligodendroglioma. The primary sites of the brain metastases were diagnosed in the lungs ($n = 10$), gastrointestinal tract ($n = 4$), breast ($n = 3$), and kidneys ($n = 2$). Two patients had melanoma as a primary origin of the brain metastases.

All the examinations were performed under similar conditions. The fluid was examined immediately after lumbar puncture procedure or was frozen in -70°C . The enzymatic activities of LDH in the serum and CSF were measured by centrifuchen analyser model 500 with kits of Boehringer Mannheim GmbH, West Germany. Relative activity from the various bands were examined by densitometer scanning Quick Quant II T Helena laboratories.

The statistical analyser employed methods of one way analysis of variance, pair-wise comparisons among groups (Benferroni test) and correlation with variables (Pearson).

Results

The mean ratio of LDH 1 to LDH 2 in CSF was found to be less than one in patients with carcinomatous meningitis, 0.653 (0.24), and in patients with cerebral metastases, 0.82 (0.109). In patients with primary benign or malignant tumours, as well as in all patients of the control group, the CSF-LDH 1/LDH 2 ratios were greater than one (table).

The CSF-LDH 1/LDH 2 ratio was found to be significantly smaller in carcinomatous meningitis and intraparenchymatous brain metastases compared to all other groups ($p < 0.001$). The CSF-LDH 1/LDH 2 ratio in carcinomatous meningitis was significantly smaller than in secondary brain tumours ($p < 0.005$). The CSF-LDH 1/LDH 5 ratio was found to be significantly smaller in

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Table CSF-LDH level and isoenzyme LDH 1/LDH 2 ratio and LDH 1/LDH 5 ratio—mean concentration

		Ratio 1 : 2	Ratio 1 : 5	LDH level (u/l)
Brain tumours	Primary benign tumours	1.1 ± 0.1	7.0 ± 0.1	29.4 ± 22.4
	Primary malignant tumours	1.2 ± 0.2	6.9 ± 1.2	239.6 ± 20.1
	Brain metastases	0.8 ± 0.1	6.5 ± 2.1	41.0 ± 7.5
	Carcinomatous meningitis	0.6 ± 0.2	3.2 ± 3.8	262.6 ± 204.2
Control group	Epilepsy and degenerative diseases of CNS	1.1 ± 0.0	5.4 ± 2.1	16.2 ± 7.90
	CVA	1.1 ± 0.1	5.5 ± 0.7	41.6 ± 18.8
	Viral meningitis and meningoencephalitis	1.2 ± 0.1	8.0 ± 0.2	19.1 ± 15.6
	Intervertebral disc herniation	1.2 ± 0.1	9.6 ± 0.0	12.0 ± 8.50

carcinomatous meningitis (3.250 ± 3.89) than in all other groups ($p < 0.001$).

The patients with carcinomatous meningitis had repeated CSF examinations at the beginning and the follow up period. In three out of four patients, the CSF-LDH 1/LDH 2 ratios at the initial stage of the disease were smaller than one. The CSF-LDH 5 ratios were normal and the cytopathological findings were negative. Subsequently, six weeks later the CSF-LDH 1/LDH 2 ratios continued to be smaller than one but the CSF-LDH 1/LDH 5 ratios became pathological and the cytological examinations of those samples were found to be positive. In the fourth patient, the ratio CSF-LDH 1/LDH 5 was greater than 15% and the cytological examination was positive at the first CSF examination. No extra fractions near the LDH 2 and LDH 3 locations¹²⁻¹⁴ were found. The serum LDH levels and their isoenzymatic pattern were normal in all samples.

Discussion

A typical distribution of LDH isoenzymes in the CSF is characteristic of several neurological diseases. Elevation of LDH 5 was found in bacterial meningitis¹⁵ and carcinomatous meningitis.¹⁶ A high level of LDH 1 was observed in fulminant bacterial meningitis with severe brain damage¹⁵ and even in viral meningitis.¹⁵ Only few studies examined the LDH isoenzymatic pattern in the CSF of various brain tumours.^{13,18} Some of these studies showed CSF-LDH 5 elevation in brain malignancy. No publications reported atypical CSF-LDH 1 and LDH 2 pattern or a change in the ratio between them in brain tumours.

In this study, the ratio LDH 1/LDH 2 < 1 was found to be significant for carcinomatous meningitis and intraparenchymatous brain metastases. This finding led us to the presumption that a similar mechanism is involved in both disorders. The mechanism is probably related to the infiltration of the leptomeningeal system of malignant cells in carcinomatous meningitis as well as in secondary brain tumours. It is worth noting that in three out of four patients with carcinomatous meningitis, the CSF-LDH 1/LDH 2 ratio changings preceded changes in the LDH 1/LDH 5 ratio and the evidences of malignant cells in the cytological CSF examinations.

A similar observation of an elevated biochemical tumour marker in both groups—carcinomatous meningitis and brain meta-

stases—without laboratory evidences of leptomeningeal dissemination was reported in CEA levels in CSF.^{17,18} The possibility of submeningeal or subependymal infiltration of tumour cells as the reason for this finding was discussed.

It is also worth noting that our main finding shows pathological changes between fractions LDH 1 and LDH 2 which are synthesised mainly in the brain tissue.^{5,19} This contradicts previous assumptions which maintained that the changes in CSF-LDH isoenzyme pattern in carcinomatous meningitis were caused by the high macrophage activity which is manifested by the increase of the CSF-LDH 5 fraction.

On the basis of these results yielded by this study, it appears that the CSF-LDH 1/LDH 2 ratio is a more sensitive parameter for carcinomatous meningitis or cerebral metastases than LDH 1/LDH 5 ratio, especially in the early stages of the disease.

Examination of CSF-LDH 1/LDH 2 ratio may be an additional useful and practical routine test for diagnosis of carcinomatous meningitis or brain metastases from solid tumours. Nevertheless, examination was limited to only four patients with carcinomatous meningitis, all of whom had a pulmonary primary demonstrating the need for further investigations of this type.

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