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Serial lumbar and ventricle cerebrospinal fluid lactate dehydrogenase activities in patients with leptomeningeal metastases from solid and haematological tumours

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SUMMARY Lactate dehydrogenase (LDH) activities were measured in cerebrospinal fluid in 350 patients with various neurological diseases to establish the sensitivity and specificity of the CSF LDH as a marker for the diagnosis of leptomeningeal metastases. Slight elevations of CSF LDH were observed in nonmalignant diseases, while marked elevations were observed in a considerable number of patients with bacterial meningitis. A sensitivity of 79% and a specificity of 83% were calculated. In the 34 patients with leptomeningeal metastases from solid and haematological tumours, the LDH in lumbar and ventricular CSF were measured simultaneously. The lumbar CSF LDH concentration in patients with leptomeningeal metastases was about five times greater than that in the ventricular CSF. No relationship was found between the CSF LDH and histology of the primary tumour. A good correlation was demonstrated between the lumbar CSF LDH and the effected area of the neuraxis. Serial determinations of CSF LDH showed a relationship between level changes and responses to therapy or progression. The findings of this study indicate that measurement of LDH in CSF can be used as an adjunctive diagnostic test for leptomeningeal metastases and in monitoring the efficacy of treatment.

Changes of biochemical markers in tissues, body fluids and serum may be used in the diagnosis of some types of cancer.[1-3] However, the clinical significance of biochemical marker tests in the cerebrospinal fluid (CSF) in the diagnosis of central nervous system (CNS) tumours is still poorly defined.[4] Moreover, various CSF biomarkers have been found to be elevated in a substantial number of non malignant disorders.

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In this paper we discuss the change in the lactate dehydrogenase enzyme (LDH) activity in the CSF, found in patients with metastatic and non metastatic diseases of the CNS. The choice to study the CSF LDH enzyme is related to the fact that LDH belongs to routine laboratory determinations and with modern equipment, the catalytic activity of LDH in the CSF can be measured rapidly, precisely and economically.

LDH is an enzyme that catalyses the final step in the metabolic chain of anaerobic glycolysis. Its molecular weight is 135,000 Daltons and it is predominantly located intracellular. LDH is a normal constituent of brain tissue and low activity can be measured in normal CSF. CSF LDH activity may increase in a number of conditions. Diagnostic significance has been ascribed to elevations of CSF LDH activities in cases of cerebrovascular diseases,[5-7] bacterial mengingitis,[8-10] head injury,[6] primary brain tumours,[7 11 12] and CNS metastases from

solid[7 8 11 12] or haematological malignancies.[8 9] Little is known, however, about the quantitative meaning of such elevations, especially regarding the usefulness of this marker in the diagnosis of leptomeningeal metastases.

To our knowledge the serial measurements of LDH in lumbar and ventricular CSF before, during and after treatment, have hitherto been unreported. In the present study we analysed the results of CSF LDH measurements at different levels of the neuraxis in patients with metastatic and non metastatic neurological diseases to determine: (1) the sensitivity, specificity and the predictive values of the LDH level in the CSF as tumour marker test, (2) the relationship between the pretreatment level of LDH in the CSF and the extent of the disease, and between that level and the histological type of the primary tumour, (3) the concentrations of the LDH in lumbar CSF related to ventricular CSF simultaneously, and (4) the correlation of serial ventricular CSF LDH changes with changes in the clinical disease status.

Patients and methods

CSF was obtained by lumbar puncture, which was performed as a part of the regular clinical diagnostic procedure, and never for the measurement of the LDH activity only. All the CSF examinations included protein concentration and glucose content, bacteriological culture, and cytological studies with the cytocentrifuge technique. The 350 patients (table 1) with an average age of 54·4 years, range 15–92 years, were admitted to the Department of Neurology of the Slotervaart Municipal Hospital and to the Antoni van Leeuwenhoekhuis, both in Amsterdam, during 1981 to 1983. There were 198 females and 152 males. The CNS metastases were diagnosed by computed tomography (CT), myelography and the presence of tumour cells in the CSF. The demonstration of malignant cells in the CSF was required for the diagnosis of leptomeningeal metastasis. In two patients, with characteristic clinical manifestations of leptomeningeal metastases, repeated lumbar CSF examinations failed to demonstrate malignant cells. The diagnosis was confirmed at a postmortem examination. In two other patients CSF cytology became positive later on in the course of the disease. Histopathological studies of the brain were obtained at 15 necropsies and did confirm the clinical diagnosis of brain metastases in nine patients and leptomeningeal metastasis in six patients, respectively.

In 23 patients of the solid tumour group and in eight patients of the haematological tumour group, neither neurological examinations including CSF analysis, nor CT brain scans or myelograms were indicative of CNS metastases. In 26 patients with brain metastases from solid tumours, the diagnosis was confirmed by CT brain scans. In 17 patients with solid tumours and in two with haematological malignancies, myelography confirmed the diagnosis of spinal cord compression by epidural metastasis. In 34 patients with clinical evidence of leptomeningeal metastases, 25 with solid and nine with haematological tumours, this diagnosis was confirmed by positive CSF cytology or positive postmortem studies. In nine patients bacterial meningitis was demonstrated by gram stain and culture. In ten patients the diagnosis of viral meningitis was established by usual clinical and laboratory criteria such as meningeal irritation, uncomplicated clinical course, CSF mononuclear pleyocytosis, negative bacterial cultures, gram stains and normal CSF glucose and CSF total protein levels. The lumbar CSF of seven patients with meningioma and 11 with malignant primary brain tumours (glioma grade III–IV) were also studied.

In 24 (table 2) of the 34 patients with leptomeningeal metastases from solid and haematological malignancies we

Table 1 *CSF LDH levels in groups of control subjects and patients, combined positive test results according to assay for CSF LDH*

		Activity (U/l)			*Significance of difference with control group*	*Number of postive tests LDH > 26 U/l*	
Group	*No*	$\bar{x}$	*SD*	*Range*	*(p)*	*N*	*%*
Control subjects	110	10·2	6·3	0–34		3	2·7
Patient groups							
Solid tumours							
without nervous system metastasis	23	11·0	6·7	0–26		0	0
with brain metastasis	26	22·6	28·4	0–136	<0·02	6	23·1
with epidural metastasis	17	18·8	21·2	0–96	<0·02	2	11·8
with leptomeningeal metastasis	25	147·4	171·2	6–711	<0·001	20	80
Haematological tumours							
without nervous system metastasis	8	13·0	10·7	4–36		1	11·1
with epidural metastasis	2	20·0	8·5	14–26		0	0
with leptomeningeal metastasis	9	122·3	98·6	6–292	<0·001	7	77·8
Benign primary CNS tumours (meningeoma)	7	20·0	15·0	8–52	<0·05	1	14·3
Malignant primary CNS tumours (glioma grade III–IV)	11	30·8	29·9	6–115	<0·001	4	36·4
Viral meningitis	10	14·6	12·0	0–38		1	10·0
Bacterial meningitis	9	236·0	950·3	34–1432	<0·001	9	100
Cerebrovascular accident	41	31·3	33·7	2–150	<0·001	13	31·7
Polyneuropathy	10	18·6	7·8	0–35	<0·01	2	20
Head injury	42	23·3	23·8	0–132	<0·001	13	31
	34 316					27 55	

Table 2 *CSF data from all patients with leptomeningeal metastases from solid and hematological tumours*

Patient number	*Sex*	*Age*	*Histology*	*Neurological evaluation***	*Protein concentration (g/l)*	*Glucose level (mmol/l)*	*CSF evaluation tumour cells*	*Pretreatment*		
								WBCs/ cumm	*Lumbar LDH level (U/l)*	*Ventricular LDH level (U/l)*
1	F	71	Lymphoma	I + II + III	0·59	1·2	+	186	20	8
2	M	35	Lymphoma	I	0·33	3·3	+	300	6	6
3	F	70	Lymphoma	I + II	2·60	2·2	+	1532	152	80
4	M	40	Lymphoma	I + II + III	5·30	2·1	+	133	292	43
5	M	34	Lymphoma	I + II	2·30	1·4	+	210	179	30
6	M	51	Lymphoma	I + II + III	4·50	0·4	+	1515	228	48
7	M	20	Lymphoma	I + II + III	0·79	4·9	+	700	44	16
8	M	62	Lymphoma	I + II + III	0·34	3·8	+	675	62	42
9	M	52	Lymphoma	I	2·00	2·0	+	80	118	—
10	M	31	Melanoma	I + II + III	4·00	0·2	+/-§	61	184	—
11	M	64	Small cell lung carcinoma	III	1·05	3·1	+	4	32	—
12	F	49	Melanoma	I + II	1·80	2·2	+	80	40	2
13	F	33	Breast carcinoma	I	0·77	0·7	+	42	118	46
14	F	62	Breast carcinoma	I + II + III	5·10	0·9	+	10	276	86
15	F	53	Breast carcinoma	I + II + III	8·80	1·7	−*	20	532	—
16	F	48	Breast carcinoma	I + II + III	5·90	2·5	+	22	138	4
17	F	71	Breast carcinoma	I	0·56	3·0	+	1	42	—
18	F	46	Breast carcinoma	I	0·41	3·8	+	13	26	16
19	F	63	Breast carcinoma	I + II + III	2·10	0·5	+	7	346	2
20	F	56	Breast carcinoma	III	0·77	1·7	+	3	42	—
21	F	59	Breast carcinoma	III	2·80	4·2	+	24	88	16
22	F	50	Breast carcinoma	I + II + III	1·50	3·3	+	27	98	14
23	F	43	Breast carcinoma	I + II + III	4·40	3·3	+	3	482	94
24	F	72	Breast carcinoma	I	0·20	3·5	+	3	20	12
25	F	69	Breast carcinoma	I + II + III	1·32	1·8	+	22	174	12
26	F	53	Non-small cell lung carcinoma	I + II + III	0·16	4·1	+	38	6	—
27	M	55	Small cell lung carcinoma	I + II + III	1·58	2·3	+	20	142	29
28	F	47	Breast carcinoma	I	2·11	0·5	+	15	70	—
29	M	40	Melanoma	I	2·91	2·7	+	12	80	—
30	M	52	Teratoma	III	2·19	2·6	+/-§	87	90	8
31	F	50	Head and neck cancer	I + II + III	4·20	0·3	−*	5	711	8
32	F	50	Breast carcinoma	I	1·05	0·6	+	125	511	273
33	M	60	Small cell lung carcinoma	I	0·63	5·6	+	—	44	—
34	F	45	Non-small cell lung carcinoma	I	0·60	2·9		6	26	20

*Autopsy studies revealed leptomeningeal metastases.
§CSF cytology became positive later on.
**Neurological evaluation:
I = cerebral signs and symptoms; II = cranial nerve signs and symptoms; III = spinal signs and symptoms.

were able to measure the LDH in lumbar and ventricular CSF subsequently, in the same session. These patients were treated with intraventricular methotrexate (MTX) via an Ommaya reservoir.[13] The CSF was withdrawn from the lumbar and ventricular spaces before treatment was initiated.

The patients with leptomeningeal metastases were divided into three anatomical categories based on their neurological signs and symptoms (table 2): (1) brain, (2) cranial nerves, and (3) spine. The extend of the tumour growth was indicated by different neurological signs and symptoms, belonging to one or more anatomical category. We have treated the patients with leptomeningeal metastases with intraventricular MTX or with whole brain radiation followed by intraventricular MTX.[13]

The criteria improved, stable and progression, were used for tumour response. Improved was defined as the disappearance of all signs and symptoms: disappearance of malignant cells was not necessary. Stable was defined as no changes in neurological signs and symptoms during therapy. Progression was defined as an increase of neurological signs and symptoms or the appearance of new lesions. The duration of the response was determined from the onset of the treatment to relapse.

LDH levels were determined in CSF using commercially available tests.[14] The test methodology of the ACA (Dupont Company, Clinical Systems, Wilmington DE, USA) is a modification of the enzymatic lactate to pyruvate procedure modified by Gay, McComb and Bowers.[15] As the method described by the Deutsche Gesellschaft für Klinische Chemie[14] in our laboratory is considered to be the reference method, the ACA method was calibrated to give results comparable with this method.

Statistics

From the results of preliminary analysis, it was decided to transform the LDH logarithmically prior to the final statistical analysis in order to obtain closer approximation of the variation of observed values by the normal distribution in all groups. Ordinary linear regression analysis was used to

determine the relationship between the log LDH level and sex and age. To test the statistical distribution of values for normality, the Shapiro and Wilk test was used. Standard methods of statistical analyses were used to evaluate the results, including Student's t test and analysis of variance and covariance. The sensitivity and specificity were calculated according to Griner *et al.*[16] Normal values were estimated from patient data using a Bhattacharya plot as described by Naus *et al.*[17]

Results

The data obtained from controls and patients are summarized in tables 1 and 2. Reference values for lumbar CSF LDH were calculated from results obtained in routine CSF analyses during a period of 34 months. Based upon 1949 patients we found a reference range from 0–26 U/l.[18] The mean CSF LDH levels of the control subjects were 10·2 U/l with a standard deviation of 0·63 units. In this group statistical analyses were carried out to detect relationships between CSF LDH activities and age or sex. From ordinary linear regression analyses we found a non linear relationship between CSF log LDH and age (p quadratic 0·036). Inspection of these figures suggests a difference between CSF LDH and the age groups of under and over 70 years. In subjects aged 70 years and older we measured no CSF LDH less than 5 U/l. This estimated difference between the two age groups was not related to sex ($p = 0·94$). We found no relationship between females and males and CSF log LDH levels ($p = 0·067$), and we calculated a deviation from normal in the control subjects at a level of $p < 0·01$. The upper nornal limit for CSF LDH activity was established as 26 U/l. In the controls the CSF LDH was elevated in three cases. Table 1 lists the positive results in patients with metastases and primary CNS tumours and non malignant neurological diseases according to assay for CSF LDH. The catalytical activity of total LDH was elevated in 27 of the 34 patients with leptomeningeal metastases from solid and haematological tumours, but also in 55 of the 317 patients without leptomeningeal metastases. On the basis of these data, the sensitivity of the test for leptomeningeal metastases was 79%, and the specificity 83%. The predictive values of positive and negative LDH tests were 33% and 97%, respectively (table 3).

We simultaneously measured the LDH activities in lumbar and ventricular CSF (table 2) and found a mean concentration of LDH in the lumbar CSF of 177·88 U/l and in the ventricular CSF of 38·13 U/l. The calculated mean lumbar LDH activity was approximately five times greater than the ventricular CSF LDH activity.

In table 4 we show the relationship between lumbar and ventricular CSF LDH and the different area of the neuraxis involved in the leptomeningeal disease. Greater tumour size (including the anatomical areas 1 + 2 + 3) correlated with higher levels of the CSF LDH at the lumbar space. There was no association with the ventricular CSF level. When only the area of the spine is clinically involved (3), the lumbar CSF LDH concentration was greater than the ventricular CSF LDH concentration ($p < 0·03$). In clinical involvement of the leptomeinges of the brain and cranial nerves (1 + 2) the ventricular CSF LDH level was higher than the ventricular CSF, taken from patients with spinal leptomeningeal metastases (area 3).

The CSF LDH activities in several types of primary tumours are summarised in table 5. There was no relationship between the CSF LDH level and the his-

Table 3 *Sensitivity, specificity and predictive value examination for leptomeningeal metastases*

		Disease			
		Present	*Absent*		*Predictive value*
Test	Positive	27	55	82	Positive test = $\frac{27}{82}$ = 33%
	Negative	$\frac{7}{34}$	$\frac{261}{316}$	$\frac{268}{351}$	Negative test = $\frac{261}{268}$ = 97%
	Sensitivity =	$\frac{27}{34}$ = 79%			Specificity = $\frac{261}{316}$ = 83%

Table 4 *Relationship between the lumbar and ventricular CSF LDH and the anatomical site of the leptomeningeal metastases*

Neuroanatomical site neurological evaluation	*Number of patients*	*Mean LDH lumbar CSF*	*Mean LDH ventricular LDH*
1	11 } 14	102·29	48·5
1 + 2	3 }		
3	4	63·00	12·0
1 + 2 + 3	16	233·44	26·92

Table 5 *Relationship between the lumbar CSF LDH level and the histological type of the primary tumour in patients with leptomeningeal metastases*

Primary tumour	*No*	*LDH elevated*		*mean*	*range*
Breast	15	12/15	80%	192·87	20–582
Non-Hodgkin's lymphoma	9	7/9	78%	122·33	6–292
Lung	5	3/5	60%	50·00	6–142
Melanoma	3	3/3	100%	101·00	40–184
Various	2	2/2	100%	405·50	90–711
Reference range Mean ± SD		0–26 U/l			

tology of the primary tumours.

Table 6 gives the relationship of serial LDH levels in the ventricular CSF to the pretreatment value and clinical response to therapy. A good correlation between decreasing LDH levels and response to chemotherapy was suggested. CSF LDH levels returned to normal values in 11 (69%). In five patients with decreased CSF LDH levels we found a progression of the clinical signs and symptoms. The CSF LDH increased in three of the 11 non-responders. In five unchanged CSF LDH levels there was a progression of the neurological disease in three cases.

Discussion

Leptomeningeal metastasis has been reported with an increasing frequency, especially in breast and lung cancer and lymphoma,[19-23] probably because of better control or early systemic disease and accompanying prolongation of survival by combination chemotherapy.[24]

The diagnosis of leptomeningeal metastasis is based upon the demonstration of malignant cells in the CSF. However, the incidence of positive CSF cytology findings in the first sample may only be 40–60%[25] and in approximately 4–5% of patients even repeated lumbar CSF examinations fails to demonstrate malignant cells. Because of negative cytological findings, the diagnosis may be delayed. Early diagnosis, however, is particularly important since there is evidence that early treatment may improve results of treatment.[1 13]

The application of tumour markers has been discussed for the diagnosis leptomeningeal metastasis.[4 26-28] We have previously reported on the usefulness of the biochemical CSF markers β-glucuronidase, β2-microglobulin and carcinoembryonic antigen[29-31] in the detection of leptomeningeal metastasis. Reports concerning the presence of LDH in the CSF of various neurological diseases, including primary and metastatic CNS tumours, have been published since 1956.[6 9 11 33] However, those studies are not uniform. Methodologies of measurements do not always meet with the optimal recommendations of to-day.[34 35]

More recent studies[36 37] have only dealt with CSF LDH activities of affected patients and did not incorporate an adequate control group. For a proper diagnostic test control subjects should reflect the group of patients with a high probability of having the disease in question. In patients with leptomeningeal metastases the differentiation must be made from cerebral metastases[38 40] and several types of infectious meningitis. In patients with spinal symptoms caused by leptomeningeal involvement from malignancies the differentiation must be made from bone and epidural metastases and non malignant conditions such as polyneuropathy, root lesions caused by herniated intervertebral disc and Guillain Barré syndrome.

Galen and Gambino[41] have published criteria for the evaluation of clinical laboratory tests used for

Table 6 *Relation of serial ventricular CSF lactate dehydrogenase (LDH) change with criteria of response to therapy in patients with leptomeningeal metastases*

Relation with pretreatment LDH	*Number of patients*	*Correlation with clinical disease status*		
		Improved	*Stable*	*Progression*
Ventricular LDH level				
Decreased	16	11	0	5
Unchanged	5	1	1	3
Increased	3	0	0	3
	24	12	1	11

diagnostic purposes. This model may only be applied when sufficient data are available for the calculations of sensitivity, specificity and predictive value of the test.

In the previous reports, the reference populations used to calculate the limits were not always free of disease. Moreover, few authors adjusted the normal range for the factors that might influence the test results other than disease. Normal values of many variables are affected by the age of the subjects. Although the earliest studies of CSF LDH did not separate normal values by age,[6 42] later studies[43 45] showed that normal values were age related. Hain *et al*[44] reported a linear increase of LDH with age. This increase was linear to the age of 70 years and then it remained constant till the age of 90 years. Spolter *et al* published a study of age related LDH activities and found a CSF LDH increase with increasing age of patients. We found, however, a non linear relationship between CSF LDH activities and age. This relationship was based upon the absence of CSF LDH activities < 5 U/l in the patients aged 70 years and older. In the patients aged 70 years and older the CSF LDH increased significantly ($p = 0{\cdot}002$). Because our group contained only three patients over 70 years of age only, we did not standardise for age.

We found elevated CSF LDH levels in leptomeningeal disease from solid and haematological malignancies and in malignant primary brain tumours. The number of patients with leptomeningeal metastases, who had negative cytologic results, have been evaluated. We found two patients with persistently negative cytology but highly elevated LDH activities. The diagnosis leptomeningeal metastasis was confirmed at necropsy. In non malignant conditions the CSF LDH was elevated in cerebrovascular accidents, in head injuries and in bacterial meningitis. Except the patients with bacterial meningitis, the degree of elevation of CSF LDH activity in leptomeningeal metastases was usually more than five times the non malignant conditions. These data indicate that an elevated CSF LDH level of approximately five times the mean activity of the control group is highly related to the diagnosis leptomeningeal metastasis.

The differentiation of leptomeningeal metastasis and bacterial meningitis might be made by the CSF white blood cell counts and culture. The CSF white blood cell counts in leptomeningeal metastases from solid tumours are usually less than 100/mm^3, while in bacterial meningitis they are greater than 100, usually in the range of 1000 to 10 000/mm^3.[46]

We found that the lumbar CSF LDH concentration was about five times greater than ventricular CSF LDH concentration. These differences in lumbar and ventricular CSF LDH at these different levels of neuraxis have not previously been described. A possible explanation might be a higher concentration of LDH in the CSF in proximity to the leptomeningeal site of involvement.

Virtually no data are available regarding changes in CSF LDH activity as a function of clinical status or treatment in patients with leptomeningeal metastases. Efficacy of treatment can be evaluated by clinical parameters and following the presence of tumour cells in the CSF. Frequently the clinical evaluation may be difficult especially if neurological improvement cannot be expected to occur due to irreversible damage to the nervous tissue. In these patients tumour response will be assessed by following CSF parameters including tumour cells. However, CSF levels of protein, glucose and malignant cells can differ at different anatomical levels of the neuraxis in patients with leptomeningeal metastases. This means that ventricular CSF may be negative while at the same time lumbar CSF contains tumour cells. We therefore analysed the relationship between the serial ventricular CSF LDH in patients with leptomeningeal metastases and the results of treatment. Our analysis shows a moderate correlation between serial ventricular CSF LDH level changes and positive response to therapy or progression of disease

This study indicates that the LDH assay of cerebrospinal fluid can be used as an adjunctive diagnostic test for leptomeningeal metastases if the clinical condition is carefully evaluated and appropriate caution is exercised in interpretation. Furthermore, serial ventricular CSF LDH measurements may be useful for monitoring the response to therapy.

More studies are needed to evaluate the use of multiple sequential tumour markers in the CSF, in monotoring patients with leptomeningeal metastases from solid and haematological tumours.

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