Lactate dehydrogenase and aspartate transaminase of the cerebrospinal fluid in patients with brain tumours, congenital hydrocephalus, and brain abscess

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SYNOPSIS The diagnostic value of CSF lactate dehydrogenase and aspartate transaminase in cases of brain tumours (except for CSF AST in the benign tumours), congenital hydrocephalus, and brain abscess is established. Tumour cyst fluids show a higher enzymatic activity than does the CSF. The two enzyme estimations do not help in differentiating the supratentorial from the infratentorial tumours. CSF AST is superior to CSF LD in discriminating the malignant and benign tumours, in so far as the AST is increased selectively in malignancy. Estimates of CSF LD are slightly superior to those of CSF AST, both in incidence of abnormality and the degree of their rise.

Reports on lactate dehydrogenase (LD) and aspartate transaminase (AST) (formerly termed glutamic oxalacetic transaminase) activities of the cerebrospinal fluid (CSF) in patients with brain tumours are not uniform, and study of these enzymes in the CSF in congenital hydrocephalus and brain abscess has not been done. Fleisher *et al.* (1957) found normal CSF LD and AST activities in 20 patients with CNS tumours, including four metastatic carcinomas. The normal CSF LD (Jakoby and Jakoby, 1958) and CSF AST (Green *et al.*, 1957; Mann *et al.*, 1960) in various types of brain tumours were also noted subsequently. However, Green *et al.* (1958, 1959) recorded a rise of both enzymes in the CSF in benign as well as malignant tumours. Still others emphasised the increased activity of one (Wróblewski *et al.*, 1958; Mellick and Bassett, 1964) or both (Davies-Jones, 1969) enzymes in the malignant tumours alone, which were either primary or secondary in origin. The LD activity of tumour cyst fluid has also been recorded as raised in malignant tumours (Sziłwowski and Cummings, 1961), which is said to be more marked in secondary carcinomas (Buckell *et al.*, 1970).

METHODS

The CSF LD and AST activities were estimated in 30 cases of brain tumours, 10 cases of congenital hydrocephalus, and two cases of brain abscess. The enzymes were also estimated in the cyst fluid of eight tumours of the series. The brain tumours included five astrocytomas, four medulloblastomas, four ependymomas, four tuberculomas, three brain stem gliomas, two glioblastomas, two haemangioblastomas, two tumours of the third ventricle, a craniopharyngioma, a meningioma, a cerebellopontine angle epidermoid, and a posterior fossa midline tumour. Of these, 15 were supratentorial and another 15 infratentorial. Out of 30 tumours 25 were proved by histology, and the other five (brain stem gliomas 3, tumour of the posterior third ventricle 1, posterior fossa midline tumour 1) were named and categorised according to their gross features, clinical behaviours, and investigations. Thus, apart from the tumour of the posterior third ventricle and the posterior fossa midline tumour, 20 tumours were malignant and eight benign. A parallel study on 25 neurologically normal subjects formed the basis of the normal control values for comparison.

The CSF was collected during ventriculography or pneumoencephalography in cases of the brain tumours, during iophendylate ventriculography through the widened coronal suture in cases of congenital hydrocephalus, and during incidental lumbar punc-

ture in the control cases. The LD and AST activities of the CSF were estimated by King's colorimetric methods (1960, 1965), which are still preferred over the spectrophotometric procedures when a group of tests needs to be done simultaneously; it saves time and, moreover, in the latter method an ultra-violet spectrophotometer is needed unless an instrument which will read at 365 nm is available, and temperature control may not be easy (Varley, 1969). In Varley's experience the colorimetric technique which he used correlates with the spectrophotometric at least as well as some other published variants he had tried. King's unit of LD is defined as that activity which would oxidise 1.0 μ mol lactate in one hour at 37°C and is expressed per 100 ml CSF; to convert it to international units per litre, or m-I. U/ml, it should be multiplied by two-thirds (Varley, 1969). Similarly, the unit of AST is the activity in 100 ml CSF which will transform 1 μ mol amino-acid to 1 μ mol ketoacid in one hour at 37°C under the specified conditions (King, 1960). Daly and Jordan (1959), after reviewing various units proposed for expressing the transaminase activity, suggested that King's unit be used for colorimetric determinations. The recorded data were analysed statistically; the mean, standard deviation, and confidence limits were calculated and the comparisons were made by Student's *t* test.

RESULTS

The mean LD content of the control group was 92.5 units/100 ml with a standard deviation of ± 21.0

and the confidence limits of 81.3 to 100.7 units. The mean AST value was 15.5 units/100 ml with a standard deviation of ± 4.4 and the confidence limits of 13.6 to 17.4 units.

The LD activity was higher than the upper normal limits (100.7 units) in 27 (90%) cases of brain tumours, and in all the cases of hydrocephalus and brain abscess. The AST was also raised in similar percentages of patients of the three groups, though in lesser proportions than the LD. The rise of both enzymes was uniformly higher in the tumour cyst fluid than in the CSF.

Table 1 shows statistical calculations of the LD and AST values in the various groups investigated, including the controls, whereas comparison of the groups with the controls, using Student's *t* test, is shown in Table 2. The results are significant at the 5% probability level in all the groups, except for the CSF AST values in benign tumours ($t=1.778$, $0.1 < P < 0.05$) which are insignificant. This establishes statistically the diagnostic value of CSF LD and AST in brain tumours (except for CSF AST in benign tumours), congenital hydrocephalus and brain abscess.

Table 3 compares different groups with one another, and shows the relative superiority of one enzyme over the other in the diagnosis of these groups. These enzymes are significantly higher in the brain cyst fluid than in the CSF of such tumour cases, in malignant tumours than in the benign, and in brain abscess than in the brain tumours. However, the difference between the supratentorial and infraten-

TABLE 1
STATISTICAL CALCULATIONS

Group	Number	Enzyme	Range (min.-max.) (100 ml)	Mean	SD ($\pm$)	Confidence limits
1. Normal controls	25	CSF LD	70 - 120	92.59	21.04	81.35- 100.72
		CSF AST	7.5- 25	15.55	4.49	13.69- 17.40
2. Brain tumours	30	CSF LD	60 -1420	410	300.86	285.77- 509.72
		CSF AST	7.5- 42.5	27.25	9.74	23.40- 48.85
3. Brain tumour cyst fluid	7*	Cyst fluid LD	540 -2500	1272.85	623.23	715.60-1830.10
		Cyst fluid AST	32.5- 50	39.28	6.9	33.12- 45.44
4. Supratentorial tumours	15	CSF LD	60 -1420	419.33	364.66	216.84- 620.45
		CSF AST	7.5- 42.5	25.33	10.83	19.26- 31.25
5. Infratentorial tumours	15	CSF LD	70 - 810	362.66	215.94	142.75- 381.75
		CSF AST	7.5- 42.5	29.16	8.09	24.63- 33.58
6. Benign brain tumours	8†	CSF LD	60 - 250	133.75	54.98	91.17- 182.97
		CSF AST	7.5- 30	20.62	7.67	14.10- 26.90
7. Malignant brain tumours	20†	CSF LD	70 -1420	516.50	295.54	376.91- 652.79
		CSF AST	7.5- 42.5	30.25	9.35	25.78- 34.51
8. Congenital hydrocephalus	10	CSF LD	180 - 850	545	238	374.09- 714.33
		CSF AST	25 - 57.5	40.95	11.25	32.85- 48.92
9. Brain abscess	2	CSF LD	200 -350	275	75	398.93- 948.93
		CSF AST	32.5- 37.5	35	2.5	12.53- 57.46

*Cyst fluid LD value of one case and cyst fluid AST value of another case were not considered for statistical reasons.

†Histological nature of one tumour of the posterior third ventricle and one posterior fossa midline tumour could not be ascertained.

TABLE 2
COMPARISON OF GROUPS WITH NORMAL CONTROLS

Group	Enzyme		Degrees of freedom (n1+n2-2)	t value	Probability	Conclusion
1. Brain tumours	CSF	LD	53	5.762	< 0.001	Significant
	CSF	AST	53	5.879	< 0.001	Significant
2. Brain tumour cyst fluid	Cyst fluid	LD	31	5.011	< 0.001	Significant
	Cyst fluid	AST	31	8.629	< 0.001	Significant
3. Supratentorial tumours	CSF	LD	38	3.467	< 0.005	Significant
	CSF	AST	38	3.368	< 0.005	Significant
4. Infratentorial tumours	CSF	LD	38	4.830	< 0.001	Significant
	CSF	AST	38	5.995	< 0.001	Significant
5. Benign tumours	CSF	LD	31	2.070	< 0.05	Significant
	CSF	AST	31	1.778	> 0.05	Insignificant
6. Malignant tumours	CSF	LD	43	6.402	< 0.001	Significant
	CSF	AST	43	6.475	< 0.001	Significant
7. Congenital hydrocephalus	CSF	LD	33	6.002	< 0.001	Significant
	CSF	AST	33	6.939	< 0.001	Significant
8. Brain abscess	CSF	LD	25	3.428	< 0.005	Significant
	CSF	AST	25	9.823	< 0.001	Significant

torial tumours is insignificant, and likewise the raised values of CSF LD in congenital hydrocephalus and brain tumours do not show any statistical difference. The difference between the CSF LD and CSF AST values in benign tumours is apparent in Table 2, where LD values are significantly raised above the normal figures and the CSF AST is unaltered. On the other hand, CSF AST, instead of CSF LD, estimations are helpful in differentiating congenital hydrocephalus from the brain tumours (Table 3).

DISCUSSION

Normal LD and AST activities of CSF in patients with primary brain tumours were reported by Fleisher *et al.* (1957), Green *et al.* (1957), Katzman *et al.* (1957), Wróblewski *et al.* (1957), Mann *et al.* (1960)

and Davies-Jones (1969). However, the present study revealed raised values of CSF LD and AST in 90 per cent of similar patients; those having normal CSF enzymes had mostly supratentorial tuberculomas and in one case a brain stem glioma. These results are in partial agreement with those of Green *et al.* (1958) and Mellick and Bassett (1964), because their observed frequencies of raised enzymatic activities were lower than the present ones.

The CSF LD and AST activities in both supratentorial and infratentorial tumours are significantly higher than those in the control group (Table 2), and the difference between the two groups of tumours is not significant (Table 3). This would refute the claims that the extent of increased intracranial pressure could be related to the increased enzymatic activity of the CSF. Further analysis of these tumours, with

TABLE 3
COMPARISON OF GROUPS WITH ONE ANOTHER

Groups compared	Enzyme		Degrees of freedom (n1+n2-2)	t value	Probability	Conclusion
1. CSF values and cyst fluid values in brain tumours	LD		35	3.567	< 0.005	Significant
	AST		35	3.819	< 0.001	Significant
2. Supratentorial and infratentorial brain tumours	CSF	LD	28	0.517	> 0.60	Insignificant
	CSF	AST	28	1.097	> 0.25	Insignificant
3. Malignant and benign tumours	CSF	LD	26	5.556	< 0.001	Significant
	CSF	AST	26	2.815	< 0.01	Significant
4. Congenital hydrocephalus and brain tumours	CSF	LD	38	1.448	> 0.10	Insignificant
	CSF	AST	38	3.450	< 0.005	Significant
5. Brain abscess and brain tumours	CSF	LD	30	1.768	< 0.05	Significant
	CSF	AST	30	3.091	< 0.005	Significant

regard to their benign or malignant nature, shows that CSF LD in both types is uniformly higher than the normal values, whereas CSF AST is raised in malignant tumours only. Comparison of the malignant and benign tumours with each other revealed a statistically significant difference. These findings suggest a diagnostic superiority of CSF AST over the CSF LD in differentiating the malignant from the benign tumours, since the transaminase activity is increased selectively and significantly with malignancy, although lactate dehydrogenase also shows a significant difference in its rise in two types of the tumours. The correlation between the increased enzyme activity of the CSF and the degree of malignancy of a tumour was suggested by Green *et al.* (1959), Mellick and Bassett (1964) and Davies-Jones (1969). This is partly supported by the present findings, because the highest records of the enzyme activities in the malignant tumours is not uniform. Viewing the histological types of the tumours, it appears that tuberculomas, whether supratentorial or infratentorial, are associated with either normal or a little over the normal CSF LD and AST activities. The other tumours showed varying degrees of rise of the two enzymes in the CSF which was more pronounced with LD than with AST. Thus, in general, the estimations of CSF LD are slightly superior to those of CSF AST, both in incidence of abnormality and in degree of its rise.

The lactate dehydrogenase activity of the tumour cyst fluid is regarded as a better index of the degree of malignancy than its activity in the CSF (Green *et al.*, 1958; Szliwowski and Cumings, 1961; Buckell and Robertson, 1965; Buckell *et al.*, 1970). This is supported by the present observations whereby dehydrogenase estimations in the cyst fluid of three benign tumours (colloid cyst of third ventricle, craniopharyngioma, and the epidermoid) were uniformly lower than those in the malignant tumours. However, this does not hold good for the transaminase activity, which shows overlapping figures in the two categories of benign and malignant tumours. The cyst fluid shows consistently higher enzymatic activities than the CSF.

The CSF LD and AST activities in patients with congenital hydrocephalus were significantly higher than in the normal subjects. It is interesting to note (Table 3) that behaviour of the CSF LD in congenital hydrocephalus and brain tumours is more or less similar without any statistical difference ($t = 1.448$, $0.2 < P > 0.1$), whereas CSF AST is significantly higher in hydrocephalus than in the brain tumours.

The CSF enzymes were significantly raised above the normal values in both cases of brain abscess of this series. The raised figures differ significantly from those in the tumour cases (Table 3). Although two cases of brain abscess do not form a representative

group, these preliminary observations should prompt further studies on larger series to ascertain their validity.

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