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Measurement of prostaglandin E2 in cerebrospinal fluid in patients suffering from stroke

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SUMMARY In 16 patients suffering from cerebrovascular events, prostaglandin (PG) E2 was measured in their cerebrospinal fluid and correlated with their clinical status and evolution. Prostaglandin E2 ranged from 200–3000 pg (picogram)/ml of cerebrospinal fluid. A positive correlation was found between PG E2 levels and the severity and clinical outcome of the stroke.

Prostaglandins (PG) which have different biological activities have been identified in human brain (Holmes and Horton, 1968; Pennink *et al.*, 1972). Data available at present indicate that PG synthesised in brain in vivo appear in the cerebrospinal fluid, are activately taken up by the choroid plexus and transported into the venous circulation and removed by extra-neuronal tissues (Bito, 1972a,b). Thus CSF, in contrast to plasma (Samuelsson, 1972), might be expected to contain measurable levels of PG. Several studies (White *et al.*, 1971; Denton *et al.*, 1972; Pelofsky *et al.*, 1972; Yamamoto *et al.*, 1972; Nakano *et al.*, 1973; Greenberg *et al.*, 1974; La Torre *et al.*, 1974) have shown that some of them such as PG F2 alpha are potent vasoconstrictor agents on cerebral arteries, while PG of the E type are vasodilators.

Cerebrovascular events are followed by the liberation of different vasoactive agents (Wurtman and Zervas, 1974; Lavyne *et al.*, 1975). In our study we found a positive correlation between PG E2 levels in CSF and the severity of a stroke.

Patients and methods

Sixteen patients suffering from suspected cerebral vascular events were admitted to Ichilov Hospital at random for clinical investigation. The clinical characteristics of the patients and findings of the investigations are summarised in Table 1. The mean age was 62.2 years (range 38 to 82 years). There were seven men and nine women. Eight patients suffered from hypertension, five from diabetes mellitus, three of these had both hypertension and diabetes. Two patients had a history of myocardial infarction.

The investigations included clinical examination, laboratory examination with measurement of coagulation factors, ECG, chest and skull radiographs, EEG, and isotopic brain scan in the first week and one month from the event. Four vessels angiography was done in 13 patients. Lumbar puncture was performed during the first 72 hours after admission for routine studies and PG E2 determination. Cerebrospinal fluid without any extraction was used for determination of PGE concentration by radioimmunoassay (Bauminger *et al.*, 1973). No drugs with known anti-PG activities were added to the treatment. The patients were treated only with Hartmann (Ringer lactate) solution and glucose 5%. Manitol and diuretics were used when necessary.

The patients were classified into two groups: (a) mild to moderate cerebrovascular accident—patients who suffered from paresis which improved during one month (five patients), and (b) moderate to severe cerebrovascular accident—patients who developed changes of consciousness and paralysis that did not improve enough during the first month (11 patients of whom five died).

The patients were followed up after the cerebrovascular event for nine to 12 months.

Results

The PG E2 levels in CSF, summarised in Table 2,

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Table 1 *Clinical and laboratory characteristics of 16 patients suffering from stroke*

Patient number	*Age (yr)*	*Sex*	*Medical history*	*Main clinical feature*	*Angiography*	*EEG*	*First brain scan*	*Second brain scan*
1	69	F	Hypertension, diabetes mellitus	Left hemiplegia, stupor, death	Right carotid occlusion	**	Mild positive	**
2	58	M	Hypertension, diabetes mellitus myocardial infarction	Left hemiplegia, coma, death	Right carotid occlusion	**	Mild positive	**
3	82	F		Right hemiplegia, aphasia, confusion, death	Normal	**	Mild positive	**
4	70	M	Hypertension	Coma, bilateral Babinski signs	Basilar artery occlusion	**	Normal	**
5	38	F		Left hemiparesis, coma, death	Normal	**	Mild positive	**
6	60	M	Hypertension, myocardial infarction	Neck rigidity, right paresis, dysphasia, confusion	Normal	**	Normal	Normal
7	72	M	Diabetes mellitus	Right hemiplegia, stupor	Normal	**	Normal	Normal
8	65	F		Meningism, Left paresis	**	**	Mild positive	Normal
9	60	F	Hypertension	Vertigo, vomiting, cortical blindness	Basilar artery occlusion	Normal	Mild positive	Normal
10	55	M	Hypertension, diabetes mellitus	Right hemiplegia, vertigo, confusion	Left internal carotid artery occlusion	**	Normal	Normal
11	36	F		Right hemiparesis, old epilepsy	Left middle cerebral artery occlusion	**	Normal	Normal
12	67	M	Myocardial infarction	Hemiparesis	Normal	Normal	Normal	Normal
13	81	M	Hypertension	Mild left hemiparesis	**	Normal	Normal	Normal
14	64	M	Diabetes mellitus	Mixed aphasia, right paresis	**	Normal	Normal	Normal
15	53	F	Hypertension	Right hemiparesis	Left middle cerebral artery occlusion	**	Normal	Normal
16	70	M		Left paresis	Normal	Normal	Normal	Normal

** = Examination not performed.

Table 2 *CSF prostaglandin E2 level and severity of stroke*

Patient number	*Severity of stroke*	*CSF*	
		Levels of PG E2 (pg/ml)	*Protein (g/l)*
1	Died	1000	8.0
2	Died	1300	6.0
3	Died	500	4.5
4	Died	200	3.2
5	Died	1500	8.8
6	Severe stroke	3000	10.4
7	Moderate to severe	500	4.0
8	Moderate to severe	350	3.4
9	Moderate to severe	720	4.2
10	Moderate to severe	215	3.8
11	Moderate to severe	200	3.7
12	Mild to moderate	200	8.5
13	Mild to moderate	100	2.2
14	Mild to moderate	150	7.0
15	Mild to moderate	150	3.0
16	Mild to moderate	150	3.6

Normal values of CSF prostaglandin E2 levels are < 70 pg/ml.
Normal values of CSF protein levels are < 4.5 g/l.

ranged from 100 to 3000 pg/ml and showed a positive correlation with the clinical outcome. The patients who suffered from mild to moderate strokes as defined above had CSF prostaglandin E2 levels which ranged from 100 to 200 pg/ml. Patients who suffered from moderate to severe cerebrovascular attacks had levels which ranged from 200 to 3000 pg/ml. Five patients died during the first month; the brain scan was moderately positive in four cases and negative in one; two showed internal carotid artery occlusion and one basilar artery occlusion on angiography, and another two patients had normal angiograms. Postmortem examination could not be done because of family resistance. Their PG E2 levels in CSF ranged from 800 to 3000 pg/ml.

Discussion

Different vasoactive agents are liberated after a cerebrovascular accident. Their exact role in the evolution of the disease has not yet been determined. These agents may be involved in the loss of autoregulation and the development of vasoparalysis. Prostaglandin E2, one of those vasoactivated agents which is present at high levels in CSF, may affect the evolution of vascular events

by inhibition of platelet aggregation and by a local vasodilator effect (Nakano *et al.*, 1972). These two biological actions may contribute to the increased hyperaemia described as the 'luxury perfusion syndrome' (Høedt-Rasmussen *et al.*, 1967; Paulson *et al.*, 1970). The inhibition of platelet aggregation and vasodilator effect of PG E2 released locally in the affected area, may cause a 'haemorrhagic infarct' and aggravate the clinical condition of the patient.

Prostaglandin E2 is synthesised from phospholipids via arachidonic acid of the cell membrane as illustrated in the Figure. It may be postulated that there is a positive correlation between the magnitude of neural tissue necrosis and the levels of PG E2, a possibility supported by the present study. From a therapeutic point of view it will be of interest to treat strokes with anti-prostaglandin drugs.

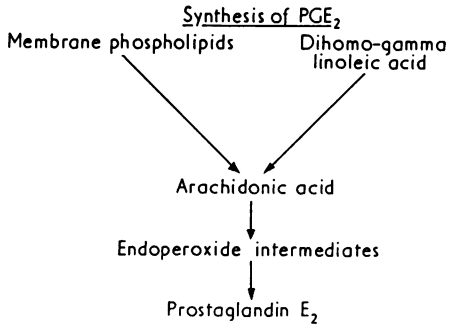

Figure *Diagram of the synthesis of prostaglandin E2.*

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