LETTERS TO THE EDITOR

Continuous intrathecal baclofen infusion alleviates autonomic dysfunction in patients with severe supraspinal spasticity

Continuous intrathecal baclofen infusion (CIBI) is a widely accepted therapy for the treatment of severe spinal spasticity. There is increasing evidence that CIBI has similar effects on patients with supraspinal spasticity resulting from either hypoxic or traumatic brain injury.¹ A proportion of patients with supraspinal spasticity present with additional autonomic dysfunction. These dysfunctions are often unresponsive to conventional antiadrenergic medication. Patients may present with severe arterial hypertension, tachycardia, hyperhidrosis, hypersalivation, and bronchial hypersecretion. Mortality is mainly influenced by these symptoms. In addition to antiadrenergic medication sedatives and analgesics are often required. During intensive care treatment such medication often leads to a prolongation of artificial ventilation and delayed rehabilitation. During rehabilitation autonomic instability additionally interferes with physiotherapeutic activity.

In the follow up of patients with severe supraspinal spasticity we noted the positive influence of intrathecal baclofen infusion on autonomic instability.¹ Study of the literature did not disclose similar findings. So far, it had not yet been pointed out that CIBI has a positive influence on symptoms originating from severe hypoxic or traumatic brain damage.

Eighteen patients with severe tetraspasticity from either hypoxic or traumatic brain injury were treated with CIBI. Before admission all patients were treated with maximum doses of various oral antispastic agents.

The interval between event and bolus test varied between 1 and 62 months (median 8 months).

After a positive response to an intrathecal baclofen bolus application a pump (Medtronic SynchroMed 8611H) was implanted for CIBI.

During the further treatment of these patients it was noted that six of 18 patients had severe autonomic dysfunction, unresponsive to conservative medical treatment (30% of the original communication¹).

Tachycardia, arterial hypertension or hypotension, often associated with agitation, hyperhidrosis, hypersalivation, and tracheobronchial hypersecretion were regarded as autonomic dysfunction associated with severe spasticity. These symptoms were graded qualitatively as not present, present and improved, or present and unchanged. This assessment was made from physicians' and nurses' documentation of symptoms in the patient files and from the observations of relatives. Due to the retrospective character of the study, a further quantitative assessment could not be performed.

Six out of the 18 patients had severe autonomic dysfunction and spasticity. Three patients had hypoxic and three severe traumatic brain injury. Two patients were severely disabled and four were in a vegetative state. The interval from primary event to pump implantation ranged from 4 to 24 months.

Table 1 Autonomic dysfunctions during the course of treatment

	Patient No					
	1	2	3	4	5	6
Tachycardia	0	+	±	0	0	+
Arterial hypertension or hypotension	0	+	0	0	0	+
Hyperhidrosis	+	0	±	+	0	+
Hypersalivation	+	+	±	0	+	+
Tracheobronchial hypersecretion	+	+	±	0	+	+
Agitation	+	+	0	+	+	+

0=Not present, +=improved, ±=unchanged.

The mean follow up was 16.8 (8-23) months and the mean daily dose of intrathecal baclofen was 408 µg (range 100-600 µg).

Four patients presented with severe spasticity (Ashworth score 5), one with an initial Ashworth score of 4 and one with an Ashworth score of 3. The following autonomic dysregulation symptoms were seen: tachycardia (3/6), arterial hyper-/hypotension (2/6), hyperhidrosis (4/6), hypersalivation (5/6), tracheobronchial hypersecretion (5/6). Agitation was seen in five of six patients. In five patients the symptoms disappeared with intrathecal baclofen therapy. In one patient (No 3), a 33 year old woman, in a persistent vegetative state after hypoxic brain injury originating from non-suicidal strangulation, the autonomic dysfunctions did not improve with intrathecal baclofen but disappeared after the additional application of intrathecal morphine. The outcome concerning the autonomic dysfunctions is shown in the table.

Patients surviving severe traumatic or hypoxic brain injury regularly have a variable period of deep coma with flexion and extension spasms and severe autonomic dysfunction that might persist over months. Later, many patients die from autonomic dysfunction or severe infections. Most of the survivors develop severe spasticity and still have autonomic dysfunction. The effects of CIBI on autonomic dysfunction have not yet been examined in the literature, although these symptoms appear in about 30% of patients with supraspinal spasticity in our series.

The patients presented had severe autonomic dysfunction and were unresponsive to conservative medical therapy. Intrathecal baclofen infusion improved most of the symptoms so that no additional medication was necessary. One patient did not improve until additional intrathecal morphine was applied. The improvement of symptoms after intrathecal morphine administration might suggest a central analgesic effect of baclofen enabling a reduction of autonomic dysfunction. Spinal inhibition of excitatory transmission might enhance the positive effect of CIBI on severe autonomic dysfunctions.

GABA-B receptors are widely distributed throughout the CNS.² The action of GABA-B receptors on autonomic regulations, especially in pathological conditions, is unknown.

Sympathetic and cardiovascular depressant effects of baclofen have been shown with local application of GABA-A and GABA-B receptor agonists and antagonists at the rostral ventrolateral medulla (RVLM) of the rat, in the cat ventromedial and posterior hypothalamus, and in isolated spinal cord preparations.³⁻⁵ However, it was possible to increase blood pressure with injection into the anterior hypothalamus and nucleus tractus solitarius.⁵

Autonomic nervous system regulation, involving different regions of the CNS, is

complex. Concerning the positive effect of intrathecal baclofen on autonomic dysfunction the findings presented should be confirmed in different clinical situations—for instance, in patients with acute midbrain syndrome. So far, we have restricted the indication for intrathecal baclofen therapy to the treatment of patients in a stable clinical condition.¹ However, after these preliminary findings we now support an early treatment to achieve an autonomic stabilisation and early prevention of contractures in patients with supraspinal spasticity.

The following conclusions can be drawn:

(1) Improvement of autonomic dysfunctions with continuous intrathecal GABA-B agonist application was achieved in all patients treated and should be considered by others.

(2) The use of CIBI offers a treatment of otherwise unresponsive autonomic instability in the acute medical setting.

(3) The pharmacological background of these findings needs further investigation. Our preliminary findings should be confirmed in pharmacological test settings.

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A new case of late onset Lafora's disease without generalised seizures

Lafora's disease is clinically characterised by the triad of epilepsy, progressive dementia, and myoclonus as well as Lafora bodies in the brain and other tissues.

The onset of this autosomal recessive disease is usually between the ages of 6 and 20 with a duration of 2-10 years. It can begin with generalised tonic-clonic seizures or focal seizures which are especially visual. Slight erratic myoclonus appears progressively with twitching movements of the fingers and facial

muscles. The EEG records show a slowing of background activity and bursts of spike and wave which are generalised, multifocal, and often sensitive to intermittent luminous stimulation. The disease provokes progressive deterioration leading to cortical and subcortical dementia and eventual death.

The cases in the literature to date, including the families which we studied, all possessed these clinical criteria.^{1,2}

The aim of this letter is to highlight one of our latest cases of late onset Lafora's disease, which occurred when the patient was 25 years old and who, although not showing evidence of either tonic-clonic or focal seizures, did, however, have dementia and erratic myoclonus over a long period. Blood taken from this patient served in the identification of the Lafora chromosome map.³

The patient was a 40 year old woman who, at 25, after giving birth to a healthy baby girl, began to show symptoms of depression and notions of persecution allied to paranoid psychosis.

At the age of 28 she came into our care with a dystonic reaction to neuroleptic treatment which affected the mouth, neck, and trunk but which cleared up when treatment was suspended. Her family informed us that the patient's condition had not improved over the previous 2 years and in addition to having memory loss she had become unable to perform normal household tasks.

The patient showed general disinterest and irritability, she was poorly oriented regarding time and space, but was, however, capable of reading, writing, and making small calculations; on the other hand she was unable to interpret a newspaper correctly or remember four consecutive words or digits. In addition, she had dysarthria and pronounced the final words of a sentence in a musical tone. She also had slight myoclonus in her hands and face. Occasionally, after a sudden stimulus she displayed myoclonic jerks in her four limbs but at no time did she lose consciousness. Generalised hyperreflexia with negative Babinsky's sign was seen. The fundus of the eye was normal.

General analysis, routine laboratory analysis, serological tests, and CSF examinations were either normal or negative, as was an EMG study. The visual, auditory, and soma-

tensory evoked potentials were all normal. Brain CT and MRI all showed evidence of a slight degree of subcortical atrophy.

The first EEG record, carried out the day after admission, showed slightly slow background activity with bursts of slow waves and paroxysms of spikes and waves. Intermittent photic stimulation induced generalised discharges of slow and sharp waves with bursts of spike and polyspike wave complexes in occipital regions. Unexpectedly, on one occasion a massive generalised myoclonic seizure with a frequency of 15 flashes/second was seen but the patient did not lose consciousness. Six subsequent records were carried out with intervals of 4 days but there was no more evidence of photoparoxysmal discharges.

Background activity continued to be slow but there were persistent discharges of slow spike wave complexes of one cycle/second and 100–200 μ V in the occipital regions.

Treatment with valproic acid and clonazepam was initiated and the patient was discharged for observation and follow up.

At the age of 29 the patient moved to her parents' home as she had become unable to carry out any housework or other household tasks, including the care of her child. A Benton and Endo test was done which showed temporal disorientation, short term memory loss, digital agnosia, ideomotor apraxia, and difficulty with reading and writing, expressive language, and logical argument. The patient could not distinguish right from left. The EEG record showed background theta activity as well as slow and sharp waves with a paroxysmal tendency. Intermittent photic stimulation did not induce further paroxysmal discharges.

During subsequent years the patient deteriorated mentally without any major epileptic seizure and only slight myoclonus. Use of valproic acid and clonazepam was suspended.

An axillary biopsy of sweat glands ruled out the presence of Lafora inclusion bodies, although a right frontal cerebral biopsy did show their presence (figure).

The patient is currently 40 years old and has obvious dementia. She moves from bed to armchair in a position of tetraparesis of limbs with pseudobulbar signs, she displays generalised rigidity with cogwheeling phenomenon and anmia, her deep reflexes are brisk, she

has only slight erratic myoclonus but no other seizures. The EEG register is slow in background activity and presents multifocal paroxysmic discharges of spike and spike waves.

In the literature about Lafora's disease, there have been few reported cases with late onset.^{4–6}

The peculiarity of our patient is that after having given birth to a child at the age of 25 she was shown to have the disease in a late onset form.

Initially she had psychiatric disturbances leading to progressive dementia with myoclonus. The patient at no point had generalised tonic-clonic or focal seizures.

Treatment with valproic acid and clonazepam was initiated as a precaution, but as the illness progressed and the patient deteriorated and still no major attacks happened, use of both was suspended. The EEGs recorded during evolution were typical with generalised paroxysmal discharges and focal or multifocal and slow background activity. The only clinical seizure that the patient presented was provoked shortly after admission and consisted of massive myoclonus with no loss of consciousness. This was caused by photostimulation in the EEG laboratory. What interested us about the patient's evolution was the evidence of dementia rather than epilepsy.

An axillary biopsy proved negative, but the cerebral cortex showed inclusion bodies characteristic of Lafora's disease, most of which were intraneuronal.

Despite the late onset of the illness in this case, studies of blood samples from the patient showed the chromosomal map of Lafora illness.

A patient with dementia and Lafora inclusion bodies but without epilepsy has only previously been described by Suzuki *et al.*⁷ This was a patient aged 59 with dementia who showed the histological findings typical of the illness. Our patient, who has now had the disease for 15 years, continues to have dementia and shows no evidence of tonic-clonic or focal seizures. Only slight myoclonus is present.

We think that Lafora's disease could be more common than previously thought and other forms of the illness should be sought, such as late onset dementia without epilepsy, accompanied or not by slight myoclonus. We also think that an axillary cerebral or other tissue biopsy, or a genetic study can show different clinical forms of the disease.

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Light microscopy of biopsy of the frontal cortex. There are characteristic intraneuronal inclusion bodies of different morphological forms with Nissl granules. Periodic acid Schiff; originally $\times 1000$.

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Abundance of left hemispheric embolic strokes complicating coronary angiography and PTCA

Stroke is a well known complication of coronary catheterisation but there are only few reports on the incidence of stroke after coronary angiography (CoAng) and angioplasty (PTCA),^{1,2} and the unique characteristics of this complication are not well documented. We therefore examined stroke rate after cardiac procedures in our institution, and whether certain stroke patterns are more common than others.

We retrospectively examined medical records of all patients that were coded in the computerised hospital database with discharge diagnoses of both stroke and CoAng or PTCA between the years 1987 and 1994. Only patients that had a stroke within 24 hours after the cardiac procedure were included. All patients were evaluated by a neurologist. The neurological deficit was classified as mild (for example, mild hemiparesis or dysphasia) or severe (for example, severe hemiparesis or aphasia). Patients with non-localising neurological symptoms such as vertigo were not included in the study. Brain CT was performed in all patients, as soon as the haemodynamic condition allowed it, for identification of haemorrhagic events. We further classified ischaemic events as embolic in patients with hyperacute presentation of stroke and maximal neurological deficit at onset. We then compared the stroke group with a control group for the frequency of cerebrovascular disease risk factors, for the

indication for the cardiac procedure, and for the degree of coronary disease that was subsequently found. The control group consisted of 48 randomly selected patients who underwent CoAng or PTCA without developing stroke. All catheterised patients routinely received antiplatelet therapy before, and heparin during the cardiac procedure. The extent of coronary disease was graded as mild (single vessel disease), moderate (double vessel disease), or severe (triple vessel disease). A χ^2 test and Fisher's exact test were used for statistical evaluation.

A total of 7151 patients underwent cardiac procedures (3460 had PTCAs and 3691 had CoAngs) during the study period. Seventeen patients had strokes that fulfilled the entry criteria, accounting for an incidence of 0.23%. Sixteen patients had an ischaemic stroke and one had a haemorrhage. The great majority of the ischaemic strokes were severe (13/16, 81.5%) and occurred during the cardiac procedure itself (12/16, 75%). All of the strokes evolved hyperacutely, with maximal deficit at onset, including those that appeared several hours after the catheterisation. Brain CT obtained in the acute phase, showed acute infarcts in the distribution of the middle cerebral artery in five patients and was interpreted as normal in all other patients. The severity, distribution, and hyperacute presentation strongly suggest that the neurological events were embolic in nature.

Stroke locations were distributed unevenly between the main vascular territories. Thirteen patients (81.5%) had a left hemispheric stroke, whereas only one patient (6%) had a minor right hemispheric event ($p < 0.0001$, χ^2), and two patients (12.5%) had a vertebro-basilar event ($p = 0.0002$, χ^2).

There were three deaths and one patient was left with severe disability. All three deaths occurred during the initial hospital stay and were related to the acute stroke.

Table 1 shows that the group of stroke patients did not differ from the control group for risk factors for cerebrovascular disease and severity of coronary disease. However, the indication for the cardiac procedure in most stroke patients was urgent (75% with unstable angina pectoris or acute myocardial infarction), whereas it was non-urgent in the

majority of controls (63% with stable angina pectoris or congestive heart failure). This difference was significant ($p = 0.01$, χ^2).

The stroke rate of 0.23% after cardiac procedures found in our study is similar to other reports.^{1,2} Identification of patients who are prone to have a stroke as well as mechanisms for its development might enable us to lower the risk of this serious complication. Brown and Topol¹ reported that stroke patients had more risk factors for cerebrovascular disease than controls. Alternatively, our study suggests that performance of cardiac procedures on an urgent basis due to acute activity of the heart disease may increase the risk of cerebrovascular complication. This may be explained by the presence of a generalised hypercoagulable state at the time of the procedure.

The clinical features of most stroke patients in our series are typical for an embolic event. Our finding that these emboli involve preferentially the left hemisphere, may provide a clue as to their source and mechanism of dislodgement. We cannot rule out completely a selection bias in this retrospective study, as minor right hemispheric events may escape diagnosis more often than left hemispheric ones. However, such a bias does not hold for major neurological events. In addition, all patients were subject to close monitoring in an intensive care setting and a consulting neurologist was routinely called in all cases of suspected neurological deficit, including minor ones, thus minimising a selection bias. Therefore, we think that the relative abundance of major left hemispheric strokes is genuine.

Uneven distribution of stroke location does not support a cardiac origin of emboli. Alternatively, brain emboli could arise in these patients from the aortic arch or carotid arteries. Such emboli could preferentially reach the left hemisphere due to the vascular anatomy of the aortic arch region. We suggest that manipulation of the catheter tip at the distal bend of the aortic arch, which is closer to the origin of the left common carotid artery, may cause dislodgement of atheromatous material preferentially into that artery. It was previously suggested that scraping the ascending aorta while searching for the ostia of coronary arteries was the cause of stroke.³ However, Tunick *et al.*⁴ showed that most protruding aortic atheromas are located distal to the innominate artery, and are therefore a cause for left hemispheric strokes in most patients. This is in good agreement with our proposed mechanism for embolism in CoAng/PTCA patients. Indeed, one of our more recent patients underwent transoesophageal echocardiography after the stroke, and an atheromatous plaque was found in the aortic arch near the origin of the left common carotid artery.

In two studies in which cardiac catheterisations were performed by inserting the catheter at a right antecubital⁵ or a brachial⁶ site, an increased incidence of vertebrobasilar strokes was found. In these cases the catheter tip may have released atheromatous material while advancing in the subclavian artery, preferentially into the vertebral system, sparing the carotid arteries. In our study, the femoral artery was used for catheter insertion in all stroke patients except for one. The one stroke patient in whom the catheter was inserted via the radial artery had a vertebro-basilar event.

In conclusion, we suggest that cardiac catheterisation still carries a measurable risk for stroke, especially in patients with acute

Comparison of clinical features between ischaemic stroke and control patients

	Stroke	Control	p Value
Number	16	48	
Male (%)	10 (62)	25 (52)	NS
Mean age (range) (y)	61 (35–81)	61 (40–80)	NS
Hypertension (%)	6 (35)	24 (50)	NS
Hyperlipidaemia (%)	9 (53)	23 (48)	NS
Diabetes (%)	5 (29)	15 (31)	NS
Smoking (%)	8 (47)	31 (64)	NS
Atrial fibrillation (%)	2 (12)	2 (4)	NS
CoAng/PTCA	10/6	24/24	NS
Indication for CoAng/PTCA:			0.01*
Urgent	12 (75)	18 (37)	
Unstable AP	10	13	
Acute MI	2	5	
Non-urgent	4 (25)	30 (63)	
Stable AP	3	29	
CHF	1	1	
CoAng/PTCA findings:			NS†
Severe CAD	4 (25)	20 (42)	
Moderate CAD	9 (56)	16 (33)	
Mild CAD	2 (12)	11 (23)	
no CAD	1 (6)	1 (2)	

AP=Angina pectoris; M=myocardial infarction; CHF=congestive heart failure; CAD=coronary artery disease.

*The number of procedures performed on an urgent versus non-urgent basis was compared between the stroke and control groups by Fisher's exact test.

†The number of patients with moderate-severe coronary artery disease versus no-mild disease was compared between the two groups by Fisher's exact test.