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Herpes zoster ophthalmicus with cerebral angiitis and reduced cerebral blood flow

L. Gjerstad¹, R. Nyberg-Hansen¹, O. Bjørland⁴,
P. Nakstad², D. Russell¹, K. Rootwelt³

Departments of ¹Neurology, ²Radiology, ³Clinical Chemistry, The National Hospital, University of Oslo, ⁴Department of Medicine, Bærum Hospital, Sandvika, Norway

ABSTRACT – Two patients with *herpes zoster ophthalmicus* (HZO) who experienced a delayed contralateral hemiparesis, the so-called crossed zoster syndrome, are described. Particular emphasis is paid to the cerebral blood flow (CBF) findings studied with the Xenon-133 inhalation technique using single photon emission computed tomography (SPECT). In a 40-year-old female with right-sided hemiparesis, angiography showed multiple segmental narrowings of the intracerebral arteries. Cerebral computer tomography (CT) scans were normal. The CBF studied 11 months after the HZO showed a generalized reduction of flow which, however, was more pronounced in the left hemisphere. On re-examination 8 months later both the mean hemispheric flow and regional CBF (rCBF) had increased to normal values. In a 66-year-old male with dysphasia and right-sided hemiparesis, cerebral CT scans demonstrated two small deep left-sided infarcts. CBF examination showed a generalized reduction of flow in the left hemisphere. The flow was slightly increased on re-examination 12 months later. These findings suggest that the Xenon-133 inhalation method represents a useful way to demonstrate the CBF pattern in this group of patients.

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Since the first description in 1896 (1) there have been more than 50 reported cases of contralateral hemiparesis following *herpes zoster ophthalmicus* (HZO), the so-called crossed zoster syndrome. The cause of the hemiparesis is believed to be viral-induced angiitis of cerebral arteries, probably resulting from direct viral invasion of the vessels (2). Autopsies have demonstrated necrotizing vasculitis of major branches of the carotid and basilar artery systems (2-4). However, thrombotic vasculopathy with occlusions of large vessels without inflammatory changes have recently also been reported (5).

Angiography in some affected patients has shown segmental narrowing of ipsilateral cerebral arteries (6), and computerized tomography of the head (CT scan) has shown changes consistent with cerebral infarction (5, 7, 8). We report two cases il-

lustrating different aspects of this syndrome with particular emphasis on cerebral blood flow (CBF) studied with the Xenon-133 inhalation technique using single photon emission computed tomography (SPECT).

CBF method

CBF was measured with Xenon-133 inhalation using a rapidly rotating single photon emission computer tomograph (Tomomatic 64)*. This method has been described in detail elsewhere (9).

Using high-sensitivity collimators, 3 slices of the brain are studied simultaneously. The slices are 2

* Tomomatic 64 manufactured by Medimatic, Inc., Copenhagen, Denmark.

Table 1
Flow values calculated from the tomograms for slice 2.

Flow study	Examin.	Mean hemispheric flow		Mean flow in ACA territory		Mean flow in aMCA territory		Mean flow in pMCA territory		Mean flow in PCA territory		FeCO ₂ (mmHg)
		Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	
Patient 1	1	44	46	40	40	46	53	45	45	42	42	42
	2	57	59	50	50	61	66	57	58	57	58	42
Patient 2	1	44	49	48	52	44	57	42	43	42	44	40
	2	47	54	51	55	48	61	44	54	45	47	39
Control mean value ± SD (No 25)		60 ± 7		56 ± 6		66 ± 8		58 ± 7		55 ± 6		41 ± 3.5
Normal right-to-left side difference (mean ± SD)		3.3 ± 2.4%		2.4 ± 3.4%		5.1 ± 3.6%		1.3 ± 4.1%		4.0 ± 3.7%		

ACA = anterior cerebral artery, PCA = posterior cerebral artery, aMCA and pMCA = anterior and posterior branches of the middle cerebral artery. Flow values are given in ml/100 g/min.

cm thick and routinely positioned 2, 6 and 10 cm above the orbitomeatal plane (OM). The resolution in the plane of each slice is 1.7 cm (full width, half maximum, FWHM).

Mean hemispheric flow was calculated from slice 2 (OM + 6 cm). The flow values in 25 normal volunteers (13 male and 12 female with a mean age of 41 ± 13 years, range 23-66 years) measured 60 ± 7 ml/100 g/min (SD) (Table 1). Flow values outside the range 46-74 ml/100 g/min were considered abnormal and were not encountered in any of the control subjects. The mean value of the normal right-to-left side difference as percentage of the highest flow value was 3.3 ± 2.4% (SD). A right-to-left asymmetry exceeding mean ± 2SD was considered abnormal.

Regional CBF (rCBF) was measured from slice 2 in areas approximately corresponding to the territories of the anterior cerebral, the anterior and posterior branches of the middle, and of the posterior cerebral artery. This was obtained by employing a software package for automatic calculation of flow values in regions of interest (ROIs). In the control subjects right-sided rCBF was slightly higher than left-sided in all 4 areas. The mean value in the 25 normal volunteers of the right-to-left side difference in corresponding areas of the 2 hemispheres as percentage of the highest value were 2.4 ± 3.4% (SD), 5.1 ± 3.6%, 1.3 ± 4.1% and 4.0 ± 3.7%, respectively (Table 1). An asymmetrical regional flow pattern was considered abnormal when it exceeded mean ± 2SD. The size of the 4 ROIs ranged from 14.0 - 29.8 cm² in the 2 patients studied. No correction was made for PCO₂ in this study.

Clinical material and results

Patient 1

The first patient was a 40-year-old right-handed woman who had systemic lupus erythematosus (SLE) complicated with cardiac arrhythmias. This condition had been treated with prednisolone for seven years when she developed left HZO with corneal involvement. Ten weeks later she suffered a right-sided hemiparesis and facial weakness which developed during a few minutes. These symptoms gradually improved but she still had a marked hemiparesis, especially in the leg, and mild dysphasia when admitted to hospital one hour later. The cerebrospinal fluid (CSF) contained no cells, the protein level was 0.49 g/l and agar electrophoresis demonstrated four oligoclonal bands in the gamma region. Cerebral CT scan without contrast was normal and intravenous digital subtraction angiography demonstrated no pathological findings of the precerebral or intracerebral vessels.

The patient was treated with dextran 40 intravenously for 3 days and she continued with prednisolone. Her symptoms gradually improved and she was discharged 3 weeks later with only a mild hemiparesis. One week later, however, she awoke during the night with left-sided headache and became somnolent. On admission to hospital a marked hemiparesis was found. Angiography of both carotid arteries and the right vertebral artery showed multiple sliceal narrowings mainly affecting the left middle cerebral artery, but also the proximal parts of the right middle and posterior cerebral arteries (Fig. 1A, B). Cerebral CT and electroence-

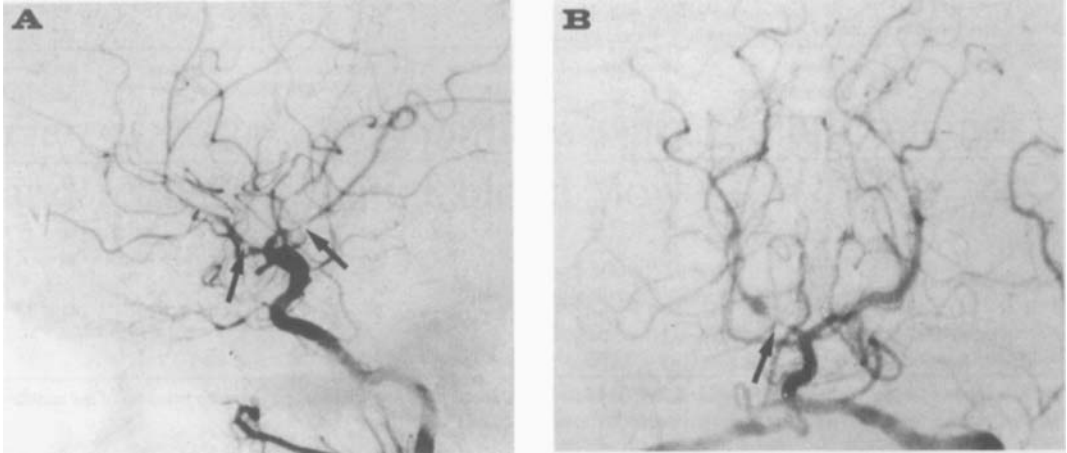


Fig. 1. Angiograms from Patient 1.

A: Carotid angiography of the left side demonstrating narrowings of the anterior and middle cerebral arteries (arrows).

B: Vertebral angiography demonstrating narrowing of the right posterior cerebral artery (arrow).

phalography (EEG) were normal. The CSF contained 4×10^6 cells/l, the protein level was 0.45 g/l and there were several oligoclonal bands in the gamma region. The varicella-zoster (VZ) antibody titre in the CSF was 160 and the ratio between the serum and CSF antibody titre was 40, suggesting intrathecal synthesis of VZ-antibodies.

The patient was treated with dexamethasone for 2 weeks, and received acyclovir 250 mg intravenously every 8 h for 10 days. Her neurological condition gradually improved and 6 months after the onset of her first neurological symptoms she had only a mild hemiparesis.

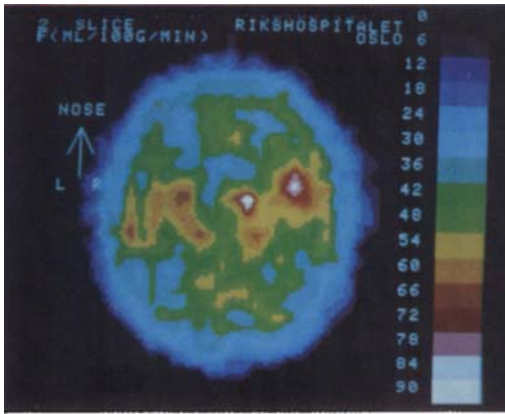
The CBF was studied 11 months after the onset of HZO and showed low flow values with a mean hemispheric flow in slice 2 of 44 and 46 ml/100 g/min in the left and right hemisphere, respectively (Table 1). Flow was lowest in the territory of the anterior cerebral artery on both sides where abnormal values were reached (Fig. 2A). There was a clear regional side-to-side asymmetry with reduced flow on the left side corresponding to the territory of the anterior branches of the middle cerebral artery. The flow was here 13% lower than in the corresponding area on the right side. In the cerebellum a crossed cerebellar diaschisis was found with reduced flow in the right hemisphere. Cerebral CT scans with and without contrast were normal and

the patient demonstrated only a moderate right-sided hemiparesis.

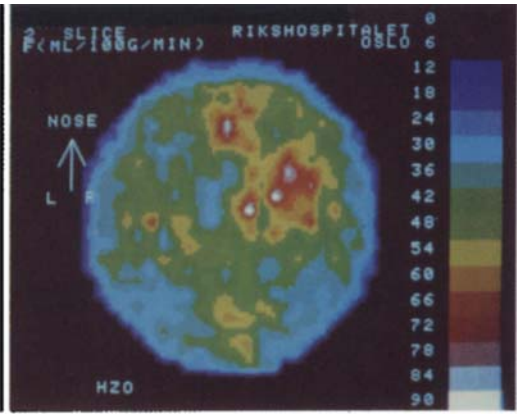
On re-examination of the CBF 8 months later, mean hemispheric flow on both sides was increased to 57 and 59 ml/100 g/min on the left and right side, respectively (Table 1). Flow was markedly increased in all areas compared to the first examination, and no significant side-to-side asymmetry was found (Fig. 2B). However, flow was lowest in both frontal regions, and a crossed cerebellar diaschisis was still present with reduced flow in the right cerebellar hemisphere compared to the left. The patient had now only a very slight right-sided hemiparesis.

Patient 2

A 66-year-old right-handed man developed left HZO with corneal involvement. Four days later he became febrile with headache and nausea. He was restless and had episodes with visual hallucinations. On Day 8 he was admitted to hospital. The CSF contained 47×10^6 cells/l and the protein content was 0.68 g/l. EEG showed generalized slow activity with focal delta waves in the left frontotemporal region. He was treated with prednisolone 20 mg daily, erythromycin and haloperidol. Prednisolone was gradually tapered off over one week. On Day 16 the neurological examination was normal except for reduced hearing on the right side. The next day



2A



3A

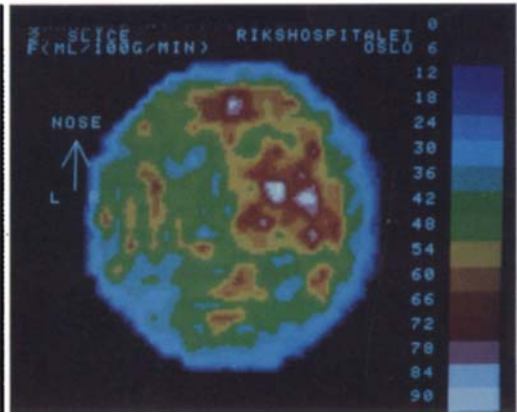
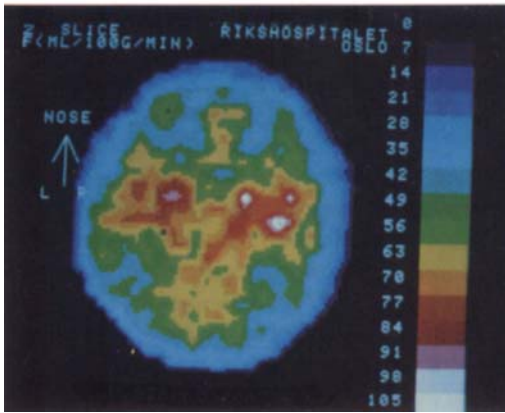


Fig. 2. CBF tomograms for slice 2 in Patient 1. A: CBF 11 months after the HZO (examination 1). B: CBF 19 months after the HZO (examination 2).

Fig. 3. CBF tomograms for slice 2 in Patient 2. A: CBF 16 months after the HZO (examination 1). B: CBF 28 months after the HZO (examination 2).

the patient suddenly developed dysphasia and a moderate right-sided hemiparesis most pronounced in the face and arm. A cerebral CT scan showed 2 small infarcts in the left internal capsule. The CSF now contained 148×10^6 mononuclear cells/l, the protein content was 0.85 g/l and the VZ-antibody titre in the CSF was 160. There were no pathological protein bands on electrophoresis on this occasion. However, 11 days later, 3-4 oligoclonal bands were demonstrated in the gamma region. No angiographical examination was performed. The patient was treated with acetylsalicylic acid and dex-

amethasone. His hemiparesis improved but he continued to have dysphasia.

When re-examined 16 months after the onset of HZO a slight dysphasia and a mild right-sided hemiparesis was found. The CSF contained 2×10^6 cells/l and a protein level of 0.52 g/l. There were no pathological bands and the VZ-antibody titre was reduced to 40.

CBF measurement showed pathologically reduced flow in the left hemisphere with a mean hemispheric flow in slice 2 of 44 and 49 ml/100 g/min on the

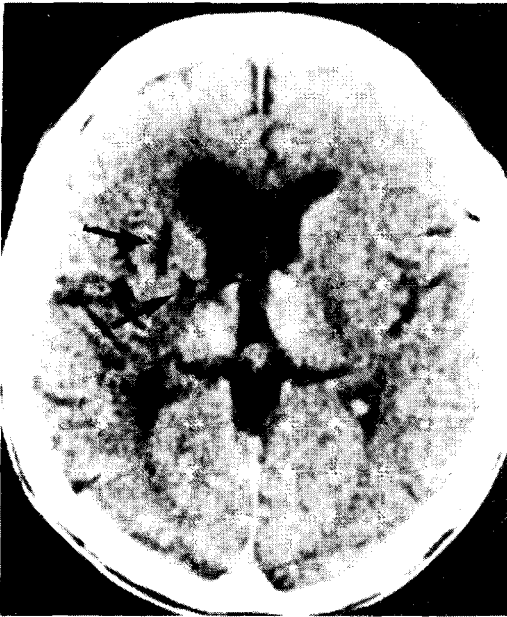


Fig. 4. Cerebral CT scan (General Electric 9800) in Patient 2 demonstrating cerebral infarction (arrows).

left and right side, respectively (Table 1). There was in addition a marked side-to-side asymmetry in the territories of the anterior branches of the middle cerebral artery with flow values 22% lower on the left side compared to the right. Flow was also low in the territory of the posterior cerebral and posterior branches of the middle cerebral artery on both sides (Fig. 3A). The low flow areas were much more extensive than the small hypodense areas found on CT scan (Fig. 4).

On re-examination 12 months later, mean hemispheric flow was slightly increased on both sides, but was still significantly lower in the left hemisphere compared to the right. The asymmetry of the rCBF was now observed in the territories of the anterior as well as of the posterior branches of the middle cerebral artery (Fig. 3B, Table 1). The flow in these areas was reduced by 21 and 19%, respectively, compared to the values in the corresponding areas on the right side. On the right side, the flow in the posterior branches of the middle cerebral artery was increased by 26% compared to the first examination. However, the CT scan findings were unchanged. The patient still had a mild dysphasia and a slight right-sided hemiparesis.

Discussion

Cerebrovascular events are well-recognized complications of herpes zoster. The contralateral hemiparesis following HZO, the so-called crossed zoster syndrome, has been reported with increasing frequency in recent years. The association may, however, be obscured by the delay between the cutaneous manifestations of HZO and the onset of cerebral symptoms. This delay may be as long as 6 months with a mean of approximately 7 weeks (10). In some patients recurrent events may occur, as in our Patient 1. She suffered SLE and used prednisolone, while Patient 2 did not have any predisposing condition for herpes zoster.

The two patients with the crossed zoster syndrome which we report are of special interest with regard to the CBF pattern. In Patient 1 a contralateral hemiparesis developed 10 weeks after the onset of her HZO, while this already occurred after 17 days in Patient 2. In addition to a generalized reduction of flow in both hemispheres, the first CBF measurement showed regional reduction of flow in areas of the appropriate hemisphere corresponding well with the clinical symptoms and signs. This was most pronounced in Patient 2 in whom the asymmetry of the rCBF was more extensive on re-examination 12 months later due to increased flow in the territory of the posterior branches of the right middle cerebral artery. However, the CT findings remained unchanged.

Furthermore, in Patient 1 the regional reduction in flow occurred without visible lesions on CT scan, and in Patient 2 the low flow area was much more extensive than the small infarcts seen on CT. This may suggest that the angiitic process of HZO does not always necessarily lead to frank cerebral infarction, but may cause incomplete ischemia and impaired neuronal function without destroying brain tissue, at least when assessed by CT. The normalisation of the flow pattern which occurred in patient 1 supports this interpretation. This makes the crossed zoster syndrome a rather unusual form of apoplexy. It differs from thromboembolic infarction with occlusion of blood vessels leading to infarction surrounded by an area with partial ischemia. In contrast to this, the angiitis of HZO may only cause partial ischemia without overt occlusion of vessels.

HZO with contralateral hemiparesis and a nor-

mal CT scan have been reported earlier (10). Angiography may demonstrate the angiitic process, but this procedure may carry an increased risk for these patients (11). Our findings stress the usefulness of CBF measurements by SPECT in order to assess and follow the cerebral blood flow in patients with angiitis affecting the cerebral vessels.

The initial generalized reduction in hemispheric flow observed on *both* sides probably reflects an extensive affection of the cerebral vessels by the inflammatory angiitic process, as partly revealed by angiography in Patient 1. Furthermore, the subsequent normalisation of flow in this patient occurring in parallel with the clinical improvement, may indicate regression of the angiitic process.

Postmortem histological examinations have shown evidence of necrotizing granulomatous angiitis of small and medium meningeal and cerebral arteries (3). It has been suggested that the HZ virus may spread from the trigeminal ganglion along the nerve fibres to the arterial walls of the middle cerebral artery and other arteries innervated by the trigeminal nerve, leading to inflammation and subsequent thrombotic occlusion of branch vessels (6). Spread along such trigeminovascular connections could explain the presence of ipsilateral infarcts resulting in hemiparesis contralateral to the HZO affection. Alternatively, the virus may spread from the trigeminal ganglion and reach the vessels via the blood or CSF as part of a more diffuse and generalized inflammatory process. This possibility may explain the bilateral vascular involvement which has been reported previously, and also demonstrated by angiography in our Patient 1. However, thrombotic vasculopathy with occlusions mainly of large vessels without notable inflammatory or granulomatous changes have recently been reported in the syndrome of contralateral hemiparesis following HZO (5). The thrombotic process may be initiated by virally induced endothelial damage (5).

The development of contralateral hemiparesis following HZO may be preceded by a more diffuse involvement of the brain with a clinical picture of meningo-encephalitis where mental changes are prominent (5, 10). This was probably the case with our Patient 2 in whom the crossed zoster syndrome occurred as early as 17 days after the onset of his HZO. He also had a mononuclear pleocytosis and elevated protein in the CSF. Patient 1 did not have

pleocytosis. However, both patients had elevated CSF VZ-antibody titers and oligoclonal bands in the gamma region, suggesting intrathecal immunoglobulin synthesis.

Improvement of the hemiparesis after the initiation of treatment with steroids has been reported in some patients with the crossed zoster syndrome (2, 11), whereas in others this has not changed the development and complications due to cerebral affection (10). The use of steroids may include a risk of dissemination of the HZV infection. Our patients were both treated with dexamethasone for 2 weeks during which they showed a slight improvement. Antiviral medication with adenosine arabinoside (6) and acyclovir (10) have been tried without apparent benefit. Our Patient 1 was treated with acyclovir and gradually improved. However, it is not clear to what extent the acyclovir therapy was responsible for this improvement. Anticoagulants have also been used in some patients and reported to be associated with a good recovery (6, 12).

Although cerebral complications due to HZO seem to have a low mortality, many patients suffer severe permanent sequelae. A more active treatment of the cerebral angiitis using both steroids and acyclovir may therefore seem appropriate. In view of the findings of large vessel thrombosis in some patients (5), anticoagulants or antiplatelet medication should probably also be given, at least initially.

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Address
Dr. Leif Gjerstad, M.D.
Department of Neurology
Rikshospitalet
0027 Oslo 1,
Norway