Cranial nerve syndrome in thrombosis of the transverse/sigmoid sinuses

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Summary
Cerebral venous thrombosis (CVT) is a cerebrovascular disease associated with a wide variety of clinical signs and symptoms, which may often delay appropriate diagnosis. Single or multiple cranial nerve palsies (III–VIII) without evidence of other signs and symptoms have not, so far, been considered a relevant syndrome of CVT. This event turned out to be a characteristic finding in five patients with thrombosis of the ipsilateral transverse/sigmoid sinus, who were recruited prospectively over a 14-month period. The diagnosis was supported by non-invasive MRI with the application of a newly developed subtraction technique. In view of the considerable mimics of this syndrome, and the long-standing need for conventional angiography to confirm the disease, it is likely to have been underestimated in the past; since appropriate treatment seems possible the diagnosis and utility of early MR venography should be considered in patients with single or multiple cranial nerve lesions of uncertain aetiology.

Keywords: cranial nerve syndrome; transverse sinus thrombosis; sigmoid sinus thrombosis; MRI

Abbreviations: aPTT = activated partial thromboplastin time; CVT = cerebral venous thrombosis

Introduction
Since the first description of a cerebral venous thrombosis (CVT) in man was diagnosed post-mortem by Ribes (1825) several case reports have been published. In the majority of patients the diagnosis was not made before pathological verification or selective angiographic confirmation. For that reason and because clinical diagnosis is difficult, CVT has been considered an extremely rare disease of a severe clinical course characterized by the presence of extensive haemorrhagic infarction and often brain oedema leading to death in most circumstances (Ehlers and Courville, 1937; Symonds, 1937; Barnett and Hyland, 1953). Since the advent of imaging techniques more favourable outcomes have been reported (Krayenbühl, 1954, 1966; Bousser et al., 1985). Computerized tomography was initially used to identify sagittal sinus thrombosis in patients with only a few, less certain, signs and symptoms if superficial cerebral haemorrhage, brain oedema and occasionally an ‘empty triangle sign’ were demonstrated (Buonanno et al., 1978; Rao et al., 1981). More recently MRI has improved the diagnostic sensitivity by simultaneous visualization of the affected brain tissue and the venous system, also demonstrating the capability of identifying transverse sinus obstructions in the posterior fossa, which represents a preferential site for CVT (McMurdo et al., 1986; Sze et al., 1988).

It became evident that the clinical syndrome no longer fitted the classical description, including signs of increased intracranial pressure in combination with cerebral/cerebellar signs, papilloedema, seizures and severe headache (Bousser et al., 1985), and might also be obscured or even oligosymptomatic if only selected veins were blocked (Jacobs et al., 1996). This is particularly so in patients with transverse/sigmoid sinus thrombosis in this first series. They presented with single or multiple cranial nerve lesions which almost always lead to another diagnosis initially.

Patients and methods
Over a period of 14 months, five patients (two female, three male; aged between 39 and 76 years) with cranial nerve syndrome of undetermined origin were prospectively studied, and MRI studies were performed systematically for identification of lateral sinus thrombosis.

All patients underwent full clinical examination, lumbar
puncture, EEG, extra- and transcranial Doppler ultrasound examinations, ECG, chest X-ray, CT and MRI. In four patients, conventional intra-arterial angio/venography was performed. Serological and haematological tests included routine blood chemistry, virus antigen or virus determination (in CSF and blood) and antinuclear antibody determination as well as further specific tests of blood coagulation, coagulation proteins and platelet function.

MRI were obtained with a 1.5-T whole body imaging system (SP 63, Siemens Erlangen, Germany) using a circular polarized head coil. Each patient underwent a routine MRI protocol with T1-proton-density and T2-weighted axial images including flash two-dimensional MR venography, post-processed by the maximum intensity projection algorithm (Mattle et al., 1991) and axial T1-weighted images after administration of gadolinium.

Additionally, we performed the new technique of digital subtraction MR venography using a pre- and post-contrast strongly T1-weighted MPRAGE (magnetization prepared rapid gradient echo) sequence described elsewhere (Fig. 1) (Neff et al., 1995).

All patients were followed for demonstration of potential recanalization by sequential re-examinations on days 21, 60, 90 and 180.

**Case histories**

For illustration of the complexity and uncertainties of the clinical diagnosis the case histories are summarized in Table 1.

**Case 1**

A 65-year-old man was admitted after 1 week of persistent vertigo, vomiting and lateropulsion with acute onset within a few hours, without progression but no relief of symptoms. The previous history was unremarkable and no hearing loss was reported.

Neurological examination demonstrated an isolated right cranial nerve lesion (VIII), consistent with delayed evoked potentials. Caloric testing revealed slowed responses, reduced on the right side to hot and cold water. There was no nystagmus and no brainstem/cerebellar signs. CT, EEG, extra- and transcranial Doppler sonography, Holter monitoring, CSF examination and routine blood chemistry revealed no abnormalities. The patient was treated with intravenous application of antivertiginosa symptomatically, but deteriorated during the following days. To exclude a small space-occupying lesion within the posterior fossa the patient underwent MRI examination; this demonstrated a thrombosis of the right transverse sinus. After effective heparin treatment, i.e. 2.0–2.5 times the upper normal activated partial thromboplastin time (aPTT) values, the patient recovered completely within 4 weeks.

**Case 2**

This 44-year-old man was admitted to our hospital 2 days after onset of diffuse mild headache with simultaneous, progressive double vision in all directions and a moderate facial palsy on the right side.

On examination, incomplete right cranial nerve lesions (III and VII) were demonstrated in the absence of other cranial nerve, motor or sensory signs. However, jerk reflexes were depressed and a mild bilateral ataxia was suggestive of Miller–Fisher’s syndrome. Examination of CSF was normal and EMG did not confirm the suspected diagnosis (lack of...
Cranial nerve syndrome in sinus thrombosis

Confirmation is not uncommon in early stages of the disease. MRI revealed a thrombosis of the right transverse sinus. After initiation of effective heparin treatment (i.e. 2.0–2.5 times the upper normal aPTT values) the symptoms disappeared within 10 days and the patient recovered completely.

Case 3
A 65-year-old woman was admitted to our hospital after subacute onset of severe vertigo, vomiting and nausea 2 weeks previously, which persisted with intermittent deterioration. One week later she noticed additional left-sided hearing loss, slight lateropulsion to the left and a complete peripheral facial palsy. Her previous history was unremarkable. In particular, there was no history of severe infection, trauma, headache or systemic illness apart from a mild cold prior to the onset of symptoms.

Neurological examination revealed complete left cranial nerve lesions (VII and VIII) with hearing loss, lateropulsion to the left, but there was no spontaneous or gaze nystagmus, even though no response to left ear caloric stimulation (33°C and 45°C water) was recorded. Papilloedema and brainstem signs were absent. Neuropsychological and behavioural examinations were unremarkable. Extra- and transcranial Doppler sonography, Holter monitoring and routine blood chemistry showed no abnormalities. Routine cranial CT excluded any space-occupying lesion within the posterior fossa. Lumbar punctures showed CSF pleocytoses (98 cells/µl), but normal total protein (37.5 mg/100 ml), and IgG, IgA and IgM levels were normal. The intracranial pressure was not elevated. The patient was initially treated for suspected post-infective multiple cranial neuritis with steroids for 5 days without any improvement; indeed, neurological symptoms deteriorated and vertigo/vomiting increased. On re-examination a lateral, mild dissociated gaze nystagmus with conjugate lateral eye movements in both horizontal directions and a peripheral benign paroxysmal nystagmus on the left-side position was demonstrated when MRI revealed a thrombosis of the left transverse sinus. After 14 days of effective anticoagulation (i.e. heparin treatment 2.0–2.5 times the upper normal aPTT values) she improved and recovered completely within the following 6 weeks.

Case 4
This 39-year-old woman was hospitalized because of a 3-week history of repeated headache, with persistent diplopia of subacute progression for a week. She had reported a history of optic neuritis 2 years before with full remission after treatment with steroids.

On examination she was normal except for a left peripheral cranial nerve palsy (VI) and slight bilateral papilloedema. Lumbar puncture and routine blood chemistry were normal. The EEG, and short latency somatosensory, visual and brainstem auditory evoked potentials, and CT scans were unremarkable. To investigate the diagnosis of multiple sclerosis further and to exclude a process within the cavernous sinus, MRI was performed, showing a thrombosis of the left transversal sinus. The patient recovered spontaneously within 1 week of heparin therapy (i.e. 2.0–2.5 times the upper normal aPTT values).

Case 5
This 76-year-old patient was admitted because of diplopia of acute onset (<24 h) 5 days previously and intermittent facial

Table 1 Neurological features, initial diagnosis and MR findings in the seven cases

<table>
<thead>
<tr>
<th>Case/sex</th>
<th>Age (years)</th>
<th>Delay in diagnosis (days)</th>
<th>Neurological features</th>
<th>Initial diagnosis</th>
<th>Suggested aetiology</th>
<th>MR diagnosis (MR follow-up)</th>
<th>CSF</th>
<th>EEG</th>
<th>Treatment/outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M</td>
<td>65</td>
<td>10</td>
<td>Right VIII nerve palsy, vertigo</td>
<td>Vestibular neuronitis</td>
<td>Unknown</td>
<td>Occlusion: right TS, partial recanalization (within 3 months)</td>
<td>Normal</td>
<td>Normal</td>
<td>Heparin/recovery</td>
</tr>
<tr>
<td>2/M</td>
<td>44</td>
<td>7</td>
<td>Right III, VII nerve palsy, headache</td>
<td>Miller–Fisher syndrome</td>
<td>Unknown</td>
<td>Occlusion: right TS, complete recanalization (within 2 months)</td>
<td>Normal</td>
<td>Normal</td>
<td>Heparin/recovery</td>
</tr>
<tr>
<td>3/F</td>
<td>65</td>
<td>13</td>
<td>Left VII, VII nerve palsy, vertigo</td>
<td>Inflammation of cranial nerve</td>
<td>Post infection</td>
<td>Partial occlusion: left TS, partial recanalization (within 3 months)</td>
<td>Abnormal*</td>
<td>Normal</td>
<td>Heparin/recovery</td>
</tr>
<tr>
<td>4/F</td>
<td>39</td>
<td>4</td>
<td>Left VI nerve palsy</td>
<td>MS, pseudo-tumour cerebi</td>
<td>Unknown</td>
<td>Partial occlusion: left TS, complete recanalization (within 3 months)</td>
<td>Normal</td>
<td>Normal</td>
<td>Heparin/recovery</td>
</tr>
<tr>
<td>5/M</td>
<td>76</td>
<td>10</td>
<td>Left VI nerve palsy, mild V irritation, headache</td>
<td>Diabetic neuropathy</td>
<td>Cholesteatoma</td>
<td>Occlusion: left TS/SS, partial recanalization (within 6 months)</td>
<td>Normal</td>
<td>Normal</td>
<td>Heparin/persistent deficit</td>
</tr>
</tbody>
</table>

M = male; F = female; MS = multiple sclerosis; TS = transverse sinus; SS = sigmoid sinus. *Cell count 98 cells/mm³ and protein 37.5 mg/100 ml.
pain and headache in the night. His medical history was unremarkable except for diabetes mellitus 10 years previously, treated with insulin. He had undergone surgery for a left mastoid infective process 10 months before.

Neurological examination demonstrated an isolated peripheral left VI nerve palsy. Blood sugar levels were slightly elevated. There were no signs of inflammation or ischaemia of the brainstem. CT excluded an orbital lesion as well as a tumour, but still showed evidence of contrast enhancement within the left petrous bone. Additional MRI was conducted to demonstrate a cholesteatoma and a thrombosis of the left transverse/sigmoid sinus was revealed in addition (Figs 1 and 2). Follow-up during a 2-month time period showed a recanalization of the thrombosis under anticoagulative therapy [first heparin, later cumarin for low dose anticoagulation INR (internationalized normal ratio) = 2], although the clinical deficit did not improve completely.

**Results**

All patients were initially suspected of suffering from other well-known aetiologies of single/multiple cranial nerve lesions. Details of their history and neurological features, MR findings and suggested aetiologies are summarized in Table 1. Diplopia, facial paresis, vertigo, vomiting, etc. resulting from involvement of cranial nerves VI, VII and VIII, which were most frequently affected, but cranial nerve palsies III and V, also occurred. Uncharacteristic associated signs were noted in all patients and consisted of headache without significant papilloedema or vertigo.

In each case the transverse and/or sigmoid sinus thrombosis was involved ipsilateral to the affected cranial nerves and correlated with the clinical signs. The venous drainage territories involved are illustrated in Fig. 3A and cover the cranial nerve topography in all cases (Fig. 3B).

The aetiology was variable, as indicated in Table 1, and covered the well-known spectrum of CVT in general including cases of unknown cause. The specific final diagnosis was only made after MRI using a pre- and post-contrast enhanced imaging technique and the conventional MR venography, always demonstrating CVT of the lateral transverse sinus. The digital subtraction MR venography was able to depict early recanalization by visualization of slow flow phenomena in the partially thrombosed sinus, associated with the recovery from clinical symptoms while undergoing treatment with effective anticoagulation.

**Discussion**

The description of CVT, as a rare disease characterized by the classical picture of headache, seizures, bilateral or alternating focal neurological deficits with frequent deterioration of consciousness to progressive coma and death, is reflected by the long-standing difficulties of diagnosis mainly based on autopsy or invasive X-ray angiography, with evidence of thrombotic occlusion of the major dural sinuses and cortical veins (Ehlers and Courville, 1937; Symonds, 1937; Barnett and Hyland, 1953; Noetzel and Jerusalem, 1965; Kalbag and Wolf, 1967).

As with other diseases, patients presenting with less severe and uncharacteristic symptoms (Averback, 1978) were only exceptionally diagnosed until the advent of non-invasive brain imaging techniques. This is reflected by a recent series which showed that papilloedema was more frequent (in up to 50%) (Bousser and Barnett, 1992) than in previous studies: 12, 34 and 43% in Gates (1986), Bansal et al. (1980) and Thron et al. (1986), respectively. The mode of onset of symptoms was also more variable than in previous studies, and the spectrum of clinical presentations extremely wide. Therefore, Bousser and Barnett (1992) in their recent review suggested separating CVT into the following four groups: those with isolated intracranial hypertension, others with

![Fig. 2](image1.png) Thrombosed inferior petrosal sinus with venous congestion of the veins in the cerebellopontine cisterna crossing cranial nerve VI (Case 5).

![Fig. 3](image2.png) (A) Cranial nerve topography in relation to venous drainage of the ventral aspect of the posterior fossa (modified and complemented from A. Berenstein and P. Lasjaunias). CN III–XII = cranial nerve roots III–XII; tr.s = transverse sinus; sig.s. = sigmoid sinus; sup.petr.s. = superior petrosal sinus; pt.v. = petrous vein; a.m.v. = anterior medullary vein; l.m.v. = lateral medullary vein; p.m.v. = pontomedullary vein; a.m.p.v. = anterior medial pontine vein; tr.p.v. = transverse pontine vein. (B) Cranial nerve topography in relation to the affected venous drainage territories in all patients.
focal cerebral signs, patients with cavernous sinus syndrome and those with unusual presentations.

The cranial nerve syndrome may be allocated to the latter group. Although Ameri and Bousser (1992) reported the involvement of cranial nerves in 12% of all CVT cases, cranial nerve palsies without other focal signs due to CVT were either not observed, or not addressed at all. This is unlikely to be due to a smaller preferential incidence of lateral sinus involvement; CVT of the sagittal sinus is as frequent as thrombosis of the lateral sinuses [70% and 72%, respectively, in the series by Ameri and Bousser (1992)], but it may result from less frequent reports of isolated thrombosis of the lateral sinus (only 14%). Along with other neurological events involvement of cranial nerves is known from the older literature; in the case of thrombosis of the petrosal sinuses, it is characterized mainly by a fifth nerve palsy for the superior sinus and a sixth nerve palsy for the inferior one (Garcin and Pestel, 1949; Symonds, 1937). In patients with lateral sinus thrombosis diplopia due to sixth nerve palsy and signs of fifth nerve irritation with temporal and retro-orbital pain, it has also long been known as the Gradenigo syndrome, suggesting involvement of the nerves at the petrous apex (Caplan, 1996). Nevertheless, more recent reports refer to patients presenting with a history of cranial nerve lesions as the major neurological finding accompanying by mild cerebellar incoordination and papilloedema suggesting cerebellar infarction or posterior fossa tumour (Bousser et al., 1985; Rousseaux et al., 1988).

Reviewing the literature, cranial nerve palsies as the only clinical feature of thrombosis of transverse/sigmoid sinuses are hardly known. Kalbag and Wolf (1972) even suggested in their earlier review that 'cranial nerve palsies do not occur from thrombosis of the superior sagittal sinus alone', and already assumed that they 'may be seen if there is associated thrombosis of another venous sinus'. Indeed Klstadt (1924) and Symonds (1931) associated sixth nerve lesions with thrombosis of the inferior petrosal sinus and suggested that the lateral rectus palsy seen in 'oticic hydrocephalus' might have demonstrated the origin of this syndrome in the petrosal sinus, provided that increased intracranial pressure was present. In a further report Symonds (1952) addressed two cases of cranial nerve lesions with involvement of cranial nerves IX, X and XI, followed by a numbness on one side of the face with sensory deficit of all three divisions of the trigeminal nerve, and suggested that CVT was the source because of the presence of signs of increased intracranial pressure such as papilloedema. Among a series of 38 cases with CVT, Bousser et al. (1985) reported three cases with affected cranial nerves: a patient with a left cranial nerve palsy (III), another one with multiple cranial nerve palsies (V to X) and the third with a right nerve palsy (VI). However, similar to the first descriptions, all patients presented with further symptoms of CVT—hemiplegia, deep coma, cerebellar incoordination, headache and papilloedema—and angiograms showed transverse sinus thrombosis in combination with obstructions of superior sagittal sinuses in all cases. Thus, apart from the few anecdotal case reports, cranial nerve symptoms alone have not hitherto been reported to be caused by CVT.

Our cases represent the first series of single and multiple cranial nerve palsies from isolated unilateral thrombosis of the transverse/sigmoid sinus. Histories and clinical findings in these patients were variable and uncharacteristic and disclosed an early straightforward diagnosis. CSF and EEG did not provide specific clues and direct and indirect CT patterns like an empty triangle sign or an ischaemic/haemorrhagic area were missed. Headache/vertigo was present in all and more than one cranial nerve was affected in three out of five with preponderance of cranial nerves VI, VII and VIII. The mode of onset was acute (<48 h in three out of five) and subacute (>48 h but <14 days with some progression in two out of five). Mental changes and disorders of consciousness were absent. However, the spectrum of conditions finally suggesting a link with lateral thrombosis is identical to the well-known wide spectrum of aetiologies (Bousser and Barnett, 1992) involving infective or non-infective courses, brain tumours, anticoagulation disorders or predisposing conditions, as well as cases of unknown aetiology. The mechanisms leading to cranial nerve lesions are probably similar to those already known from sagittal superior sinus thrombosis.

From the anatomical point of view the lateral sinuses extend from the torcular herophili to the jugular bulbs. They consist of two parts, a transverse portion which lies in the border of the tentorium attached to the occipital bone and a sigmoid portion, which courses on the inner portion of the mastoid process separated by a sinus plate from the mastoid air cells and the middle and inner ear structures. The sigmoid portion ends at the jugular foramen and drains into the jugular veins. Blood from the cerebellum, brainstem and posterior portions of the cerebral hemispheres drain into the lateral sinuses. Other veins from cranial nerves in the posterior fossa, the middle ear and diploic veins also drain into the lateral sinuses. Commonly, the left transverse is smaller than the right one and is hypoplastic or absent in ~15–20% of the population.

Since upper cranial nerves occur in the territory of the veins at the ventral aspect of the brainstem, and the transverse pontine vein in particular, thrombosis of the anterolateral pontine vein and the lateral medullary vein together with the draining petrous veins and the veins of the lateral recess are potential sources of isolated cranial nerve syndromes, if the so-called 'extrinsic' system of the brainstem is affected. This lateral draining venous pathway is crucially dependent on a patent transverse/sigmoid sinus system. Venous drainage of caudal cranial nerves is separated because the lower brainstem region (below the pontine-medullary angle) depends on the caudal or medullary 'intrinsic' or longitudinal drainage system (Duvenoy, 1978; Berenstein and Lasjaunias, 1990).

Depending on the individual Anastomoses of the venous network, thrombosis of the lateral sinuses can produce a venous overload, which is well known from parenchymous
tissues, i.e. 'venous congestion'. Venous congestion differs from venous infarction and reflects reversible compromised oxygen or glucose consumption within the cortical brain tissue as a result of reduced venous drainage and vascular oedema. Oedema is probably the most common abnormality responsible for focal neurological signs and symptoms, in addition to other parenchymal abnormalities including haemorrhage and ischaemia. It may be localized to the region formerly drained by the occluded venous channel and may be increased if capillary leakage in the intertissue space occurs. This may be due either to increased local pressure or to stasis in small venules and increased capillary pressure due to backwater in the draining venous system, which is apparently the consequence of dilatation of the cranial nerve veins that serve as collateral channels between anterior and posterior venous networks. Since this capillary network shows restricted collateral capacity, local stasis may cause temporary dysfunction until thrombolysis occurs (spontaneous or probably accelerated by anticoagulation). This was seen in four out of five patients clinically and on MR in all patients reported (although treatment was not studied prospectively or blindly in a randomized series).

Considering the long-standing and still often used invasive approach to establish the diagnosis, the number of patients with selected transverse/sigmoid sinus thrombosis is probably underestimated; considering the variation of the cerebral venous system on the one hand and the illustrated isolated veins that serve as collateral channels between anterior and posterior venous networks. Since this capillary network shows restricted collateral capacity, local stasis may cause temporary dysfunction until thrombolysis occurs (spontaneous or probably accelerated by anticoagulation). This was seen in four out of five patients clinically and on MR in all patients reported (although treatment was not studied prospectively or blindly in a randomized series).

Nevertheless, MRI and MR angiography may still overlook venous obstructions of the transverse and sigmoid sinuses (Macchi et al., 1986) because of misinterpretation of the complex signal intensity pattern of flowing and clotting blood and difficulties in separating hypoplasia and aplasia. This difficulty is shared by intra-arterial angiography, and thrombotic occlusion may be misinterpreted as a variant of paired sinuses, when dilated or tortuous collateral veins (as signs of venous obstruction) are absent (Yarsagil and Damur, 1974; Osborn, 1980).

We found the application of a contrast agent to be of particular diagnostic value in our series, since post-contrast images clearly delineated the thrombosis of the sinus by enhancing the dural wall in all cases, whereas a severe pathological signal from the sinus occurred in only 42% of the cases. In addition to the conventional MR venography, the demonstration of slow flow in congested veins together with the detection of small cortical and internal venous structures is an advantage, as reported previously (Neff et al., 1995). The difficulty in interpreting the complex flow signals can be significantly reduced by combining both methods: post-contrast T1-weighted spin-echo imaging and digital subtraction MR venography.

References


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