Intracranial venous and dural sinus thrombosis due to protein S deficiency in a patient with AIDS

Protein S (PS) is a vitamin K-dependent plasma protein that inhibits blood coagulation by inactivating factors Va and VIIIa in cooperation with protein C. Deficiency of protein S, congenital or acquired, predisposes to thrombotic disease. In postmortem studies, the prevalence of cerebrovascular disease in HIV-infected patients has ranged from 11% to 34%. The causes are diverse, and include embolic and thrombotic stroke, cerebral vasculitis, and cerebral haemorrhage. Decreased free protein S has been commonly found in HIV-infected adults and has been associated with symptomatic venous thrombosis.

To our knowledge, we report the first case of an HIV-infected adult with intracranial dural sinuses and cerebral venous thrombosis due to protein S deficiency.

A 37-year-old HIV-infected woman was admitted with severe and persistent headache of two weeks duration in January 1994. She had no history of thrombotic events and there was no evidence of any precipitants of thrombosis. She had no history of thrombotic events and there was no evidence of any precipitants of thrombosis. She had never received oral contraceptives or anticoagulants. On admission, vital signs were normal and physical and neurological examinations were unremarkable.

Laboratory studies showed a white blood cell count of 1.7 × 10³/l, a platelet count of 72 mm³, and erythrocyte sedimentation rate of 10 mm/h. Biochemical indices were within the normal range. Serological tests for syphilis and toxoplasmosis were non-reactive. Tests for anti-SM, anti-DNA, anti-ENA, and anti-phospholipid antibodies (anticyclic citrullinated and lupus anticoagulant) were all negative. Prothrombin and partial thromboplastin times and albumin, fibrinogen, anti-thrombin III, and protein C concentrations were normal. Protein S concentrations, measured by a crossed immunoelectrophoresis method, were 49% (normal 60% to 100%) and 28% of normal values 65% to 125%), corresponding to free and functional protein S respectively. The family history was negative for thromboembolic disease and her parents' protein S concentrations were normal.

A urinary monoclonal antibody test concentration of 2.3 μg/ml (normal <10) excluded pregnancy. Electrocardiography and two-dimensional echocardiography did not disclose any abnormality.

Brain MRI disclosed hyperintense signals on T1 and T2 weighted images in the left venous sigmoi and lateral sinus. Findings from MR angiography were consistent with obstruction of these sinuses and of the left jugular vein (figure). The patient was initially treated with heparin and when adequate anticoagulation was achieved, heparin was gradually discontinued and long-term acenocoumarol was started. No recurrence of thrombotic or neurological manifestations have occurred during two years.

Protein S is synthesised by endothelial cells, megakaryocytes, osteoblasts, neural derived tissues, and hepatocytes. Acquired decreases in protein S concentrations have been described in liver disease, neoplastic syndrome, systemic lupus erythematosus, disseminated intravascular coagulation, warfarin and oral contraceptive therapies, pregnancy, and HIV infection. The prevalence of decreased free protein S in HIV-infected patients has ranged from 31% to 76%. HIV has been found within endothelial cells of cerebral blood vessels. Thus it has been suggested that protein S deficiency can result from abnormal endothelial cell function during HIV infection. Although the mechanism responsible for the decreased in protein S is unknown, the proinflammatory cytokine tumor necrosis factor is increased in HIV-infected patients and may induce a procoagulant state on the surface of endothelial cells, down regulating synthesis of protein S. Some authors have reported that HIV-associated protein S deficiency may predispose to deep vein thrombosis and pulmonary embolism.

Sagittal sinus thrombosis has been reported in a seronegative patient with hereditary protein S deficiency. Although cerebrovascular disease is not uncommon in patients with AIDS, only a single case of dural sagittal venous thrombosis has been reported to date, in a four month old girl born to an HIV-infected mother. Sagittal sinus thrombosis has been reported in a patient with AIDS dementia complex. The present case also suggests that long term anticoagulant therapy may prevent further thrombotic events in HIV-infected patients with this disorder.

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LETTERS TO THE EDITOR

Serious neurological manifestations of ciguatera: is the delay unusually long?

Ciguatera poisoning is the commonest fish food poisoning encountered in tropical islands, especially in the Pacific. The disease is usually benign, with gastrointestinal and cutaneous manifestations. Patients may have a delay of 4 – 12 hours, or even several days, after the consumption of fish. However, serious forms of this fish poisoning, with cardiovascular and neurological disorders, have been described. The serious forms are associated with prolonged axonal sodium channel activation, by contrast with other fish toxins (tetrodotoxin for instance), is now described as the main mechanism by most authors.

We present the results of the retrospective analysis of ciguatera cases admitted to Gaston Bourret hospital (Noumea, New Caledonia, South Pacific) between January 1991 and December 1995. Fifty six cases were reviewed (19 female and 37 male patients, mean age 37 (SD 15), range 2–62).

Diagnosis of ciguatera was made on clinical grounds—that is, history of fish eating and suggestive clinical manifestations. Two groups were established. In the first group, patients had only common signs of ciguatera poisoning including gastrointestinal (nausea, vomiting, abdominal pain, diarrhoea) and cutaneous symptoms (pruritus, itching sensation). Patients with the usual neurological complaints of ciguatera (parasthesia, muscle pain) were included in this group ("common" group). In the other ("neurological" group) patients had infrequent or severe neurological symptoms—namely, vertigo, ataxia, progressive muscular weakness or sensory loss (polyneuropathy), visual blurring, and stupor or confusion. The delay between the consumption of fish and the onset of ciguatera was known in 41 patients (seven of 10 in the "neurological" group and 36 of 46 in the "common" group). There was a significant difference in delay between the groups (46.9 (SD 20) hours in the "neurological" group and 4.8 (SD 5.2) hours in the "common" group (p=0.0084, Mann-Whitney test)). Age, sex, number of previous episodes of ciguatera, and type of fish were not significantly different between the groups (X² test).

To our knowledge, this longer delay in serious neurological cases of ciguatera has never been statistically documented, although Allsop et al reported a long delay between the first manifestations of ciguatera and the appearance of neurological signs. Further prospective studies are needed to assess this putative characteristic of "neurological ciguatera". Ciguatoxins act on axonal sodium channels and elicit a prolonged action potential. By this action, intracellular water and sodium influx could increase and induce neuronal oedema.

In vitro ciguatoxins can provoke a nodal swelling and also a large increase in inter-nodal length and volume. Changes in mem-

brane sodium current induced by ciguatoxins have been linked to these swelling effects. Slowing of nerve conduction could be explained by both changes (nodal swelling and prolonged activation). In Guillain-Barré syndrome, the delayed clinical signs may be explained by a prolongation of the sodium channel inactivation by the ciguatoxins, which is consistent with the nodal length and volume effects. However, this is the first study to show a long delay between the consumption of fish and the onset of neurological signs.
syndrome, internodal length is increased early in the disease and in experimental allergic neuritis the earliest pathological signs are breakdown of the blood–nerve barrier, oedema, and infiltration of activated lymphocytes. Also, we postulate that water and uncharged molecules (molecular weight below 600) induced by ciguatoxins could provoke secondary disturbances in nerve fibres, which would explain the long delay in "neurological ciguatera". A striking oedema of Schwann cell cytoplasm has already been reported in vivo. In this report, the axon was shown to be compressed by axonal oedema. Raised endoneurial fluid pressure induced by oedema might reduce nerve conduction velocities. Direct compressive effects or endoneurial fluid pressure could both induce nerve blood supply deficiency. Further nerve (axonal?) disturbances could be due to the ischaemic effects of oedema. In this hypothesis, neuronal oedema would have to be managed as a neurological emergency.1 Mannitol is known to be effective in the treatment of ciguatera,2 and its mode of action could be to suppress nodal swelling and sodium channel activation induced by ciguatoxins.3

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Isolated ataxia and autonomic dysfunction: a new variant of Guillain–Barré syndrome?

Several variants of Guillain–Barré syndrome have been described including Fisher’s syndrome, pure motor Guillain–Barré syndrome, pharyngeal–cervical–brachial weakness, paraparetic pattern, ataxic form, and pure pharyngeal–cervical–brachial weakness syndrome, pure motor Guillain–Barré syndrome, has been described including Fisher’s syndrome: a new variant of the adaxonal Schwann cell cytoplasm has "neurological ciguatera". A striking oedema of fibres, which would explain the long delay in phocytes. Also, we postulate that water and nerve bloodflow. Direct compressive e pressure induced by oedema might reduce aged as a neurologicalemergency.

Ischaemic e endoneurial fluid pressure could both induce practical disorder and had been developed flu-like symptoms three weeks before admission. He had a history of a bipola
diabetes insipidus and had been treated for many years with lithium, car

He was seen at the psychiatry outpatient clinic by a consultant neurologist (GT) who concluded that he had a progressive cerebel
dysfunction: a new variant of Guillain–Barré syndrome. Abnormalities in CSF and electrophysiological findings sup
dicated this diagnosis. During the full observation period ocular movements were repeat-
еды tested and always found to be normal.

As the patient’s postural hypotension did not react to symptomatic treatment, we started treatment with IVIg assuming that his disease was a variant of Guillain–Barré syndrome. After IVIg treatment postural hypotension indeed dramatically improved and did not return. The positive effect of IVIg did not diminish after a few days, suggesting a specific, immunomodulating mode of action rather than a short lasting increase in blood pressure through an increase in blood protein concentrations by high dose IVIg. A diagnosis of Guillain–Barré syndrome could not be made in our patient because he did not fulfill the diagnostic criteria of the typical syndrome.1 Intact proprioception and vibration sense combined with pronounced ataxia is accepted to be an exclusive feature of sensory form of GBS and against the sensory ganglionopathies as recently reviewed by Dalakas and Quarles.3

A combination of acute sensory and autonomic neuropathy has only rarely been described in a 26 year old woman after Cox
die B virus infection.1 However, in that case there was also pronounced impairment of cutaneous sensation and extensive muscle weakness. A Japanese patient has been described with ataxia and orthostatic hypo
tension after infection with Epstein–Barr virus.4 By contrast with our patient no CSF abnormalities were noted.

We conclude that the unique combination of ataxia without loss of proprioceptive sense and severe postural hypotension as a result of autonomic neuropathy in our patient suggests either a new variant of Guillain–Barré syndrome or a new overlap syndrome of acute pandysautonomia and acute cerebellar ataxia.

Sensory sleep starts

Sleep starts, also known as hypnic jerks, hypnagogic jerks, and predormital myoclonus, are benign, physiological phenomena. They usually present with motor manifestations of transient body jerks at onset of sleep, and are often triggered by fatigue, stress, and sleep deprivation. Sensory manifestations have been well described as accompaniments of the movements. To our knowledge, the only literature reference to sensory phenomena without a body jerk is an anecdotal comment within a review article. We now report on two patients with purely sensory complaints restricted to onset of sleep.

Patient 1, a 42 year old college professor, had a 12 year history of 5–30 s spells occurring weekly to monthly. These episodes always occurred on falling asleep. She described mild, moderate, and severe spells as follows: mild = non-radiating electric shock-like sensation in the chest; moderate = mild plus a sense of suffocation; severe = moderate plus a poorly described medial right arm, ring, and little finger numbness. After the initial sensation, she is alerted and then aware of the surroundings.

Patient 2, a 29 year old attorney had an eight year history of onset sleep spells lasting several minutes. These consisted of a focal itchy, sharp, pinprick-like sensation that may occur anywhere. The initial sensation awakens her and then the sensation shifts from one area to another for brief periods. There is no pattern to the location of the shifting. Sensations do not provide relief. The sensations may recur while attempting to fall asleep again. Episode frequency has increased from two to three times a year initially to once or twice a month. Changing skin care products, detergents, bedsheets, and clothing did not affect the episodes. The episodes occurred at home, as well as in other locations. Medical history was significant for migraine headaches without aura, not temporarily related to the sleep onset episodes.

In both patients the spells occasionally occurred during periods of daytime sleep or drowsiness. Stress, fatigue, and sleep deprivation were often provoking factors. The sleep schedules were regular and sleep was otherwise undisturbed. Family histories were unremarkable and general physical, dermatological, and neurological examinations were normal. There was no history of recreational drug use. There was no associated tongue biting, urinary incontinence, or body movements noted at the time of initial medical evaluation. At follow up, however, patient 2 had noted a brief limb movement on two interim occasions after initial perception of the sensation. She thinks that these movements were a voluntary response to the itchiness during alerting.

The following studies were normal: patient 1, ECG, Holter monitor, brain MRI, several EEGs, a prolonged daytime sleep EEG, and polysomnography; patient 2, brain MRI.

The occurrence of sensory phenomena exclusively at onset of sleep should prompt a consideration of sensory sleep starts. The differential diagnosis includes nocturnal seizures, other parasomnias, hyperekplexia, restless legs syndrome, periodic limb movements in sleep, excessive fragmentary myoclonus, exploding head syndrome, and erroneous psychiatric diagnoses. Recognition of this unusual predormital syndrome may eliminate unnecessary diagnostic testing and avoid unnecessary anticonvulsant therapy.

High concentrations of PS-1 mRNA in skin fibroblasts of patients with Down’s syndrome

The present study consisted of 12 patients with Down’s syndrome (age 32.8 (SD 25.8); eight patients with dementia and four patients without dementia); 18 patients with sporadic Alzheimer’s disease (age 57.5 (SD 24.5); six patients with mild, nine with moderate, and three with severe degrees of dementia) who had no mutation of APP, PS-1, and PS2 genes; and 22 neurological patients without dementia as controls (age 41.8 (SD 34.8)).

The diagnosis of dementia was based on interviews, medical findings, neurological examinations, cranial CT, general haematological tests, blood chemical tests, EEG, the mini mental state examination, Barthel index (daily activities), and surveillance of daily activities. Patients who carried trisomy on chromosome 21 were diagnosed as having Down’s syndrome.

Patients who satisfied the diagnostic criteria of the Down’s syndrome M-III-R and NINCDS-ADRA dementia criteria and those scoring <5 on Hachinski’s ischaemic score were diagnosed as having Alzheimer’s disease.

The severity of disease was established according to the Down’s syndrome M-III-R criteria of mild, moderate, or severe. Skin fibroblasts were prepared from the patients as follows. After the patients’ and his or her family’s consent had been obtained, skin fibroblasts were collected from the brachial skin, cultured, and incubated according to the method of Ohno et al. Northern blot analysis was performed by the method of Goldberg. We quantified the relative ratios of densities of PS-1 mRNA to β-actin mRNA using a densitometer. We evaluated differences between groups by the Mann-Whitney test.

There was no significant association between PS-1 mRNA and age in CTL. The relative ratios of densities of PS-1 mRNA to β-actin mRNA in fibroblasts of patients with Down’s syndrome were significantly higher than those of the controls (p < 0.05). However, there was no significant difference between these values for patients with moderate to severe dementia and those of the controls.

These findings suggest that the PS-1 gene may play an important part in the development of Alzheimer’s disease in the early stages, and that PS-1 may also be closely associated with dementia in Down’s syndrome. Although it is well known that patients with Down’s syndrome carry trisomy on chromosome 21, the cause for the dementia in patients with Down’s syndrome is unknown. We consider that both Alzheimer’s disease and Down’s syndrome may share the same mechanism, a high concentration of PS-1 mRNA leading to the development of dementia. Further studies are necessary to clarify the mechanisms relating to these high concentrations of PS-1 mRNA in Down’s syndrome as well as in Alzheimer’s disease.

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4 Gastaut H, Broughton R. A clinical and polysgraphic study of episodic phenomena during sleep. Recent Advances in Biological Psychiatry 1964;4:197–221.

Dysgeusia has already been reported in internal carotid artery dissection.\(^1\)\(^2\) It indicates a IXth nerve or a chorda tympani involvement. A taste deficit in the posterior third of the ipsilateral hemitongue suggests damage to the IXth nerve. The existence of a left inferior sore throat, which could correspond to the sensitive laryngeal territory of this nerve, supports such a hypothesis. Isolated dysgeusia, presumably due to chorda tympani palsy, has already been reported, but in that case, the taste deficit is supposed to involve the anterior part of the tongue; moreover, such a mechanism is unlikely in our patient, as the chorda tympani emerges from the skull by the fissura petrotympanica, which is located more than 1 cm lateral and anterior from the carotid canal.\(^3\) Therefore, dysgeusia was more probably due to direct compression of the IXth nerve by the mural haematoma seen in MRI. The lesion was located at the level of the second cervical vertebra, where the IXth nerve crosses the internal carotid artery medially (figure C).

When the IXth nerve is involved, other lower cranial nerves are usually affected, most often the hypoglossal nerve (XII).\(^4\) Nerves X and XI are the other lower cranial nerves usually involved in cases of IXth nerve palsy.\(^5\) All these nerves emerge together from the skull by the foramen jugulare and are therefore close to each other at the prepetrosal level. However, it should be noted that, at this level, the IXth nerve is closer to the internal carotid artery than the Xth and XIth nerves and, may therefore be the only nerve affected by a small mural haematoma such as that in our patient.

Dysgeusia related to an isolated glossopharyngeal palsy in a case of internal carotid artery dissection has not, to our knowledge, previously been reported. The absence of involvement of other cranial nerves in our patient may be explained by the limited...
vertical extent of the dissection, which affected only the final prepetrosal segment of the internal carotid artery at level C2. The dissection thus spared the IXth nerve, located at a lower level (third cervical vertebra), and the Vth and VIIth nerves, located at a still higher level. Furthermore, the small lateral extent of the mural haematoma would seem to explain why the IXth and Xth nerves were spared.

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Psychiatric symptoms in MELAS; a case report

Over the past years much has been clarified about mitochondrial pathology. There are several encephalomyopathies related to mitochondrial dysfunction, of which the most important are Kearns-Sayre syndrome (KSS), myoclonus epilepsy and ragged red fibres syndrome (MERRF) as well as the mitochondrial encephalomyopathic lactic acidosis and stroke-like episodes syndrome (MELAS), about which several reviews were published recently.1,2

The clinical picture of MELAS is the result of a respiratory chain defect and involves mainly the CNS and the skeletal muscles, which are especially vulnerable to mitochondrial dysfunction because of their dependency on the oxidative metabolism.3 The histopathological expression in the skeletal muscles is ragged red fibres which are caused by impaired intramitochondrial protein synthesis. The clinical expression of MELAS is highly variable, in that different mutations can lead to a similar clinical syndrome and a given mutation may be responsible for an inconstant phenotypical expression.4

In most cases, the enzymatic defect in MELAS is a complex I deficiency and, to a lesser degree, complex IV deficiency. The enzyme abnormality is associated with a point mutation at np3243 in the tRNA Leu(UUR) region, which accounts for 80% of the patients with MELAS.5

The MELAS syndrome was first described in 1984 by Pavakis et al.6 Later, Hirano and Pavakis described the target symptoms and additional clinical manifestations, based on 110 reported patients with MELAS. The six target symptoms include clinical stroke, seizures, lactic acidosis, ragged red fibres, exercise intolerance, and onset of symptoms before the age of 40. Additional clinical manifestations comprise dementia, limb weakness, short stature, hearing loss, and recurrent migraine-like headaches. Lactic acidosis is the most common finding from laboratory investigations. In 12% of patients the ECG discloses Wolff-Parkinson-White syndrome. Protein and lactate in CSF is raised in most patients. In about 80% of the patients lactic acidemia with high titers, mostly localised in one of the cerebral hemispheres, can be shown by brain CT.

Psychiatric symptoms in patients with MELAS are rarely reported. Suzuki et al described one patient with schizophrenia-like symptoms such as auditory hallucinations, delusions of persecution and disorganised behaviour.

Here we report on a female patient with MELAS in whom psychiatric symptoms preceded the establishment of the clinical diagnosis for several years.

She was admitted in December 1987 to the Vincent van Gogh Institute for Psychiatry in Venray, The Netherlands, because of aggresive and paranoid behaviour and neglect of body care. She was born from non-consanguineous parents and had a normal psychomotor development. Family history did not disclose a history of schizophrenia or psychiatric disorder. At the age of 14 she had been evaluated medically for the first time because of short stature. No abnormalities were found. The medical history comprised two previous neurosurgical procedures during hospitalisation. The first, at the age of 18, was mandated because of severe headaches, a confusional state, aphasia and apraxia. Hemiparesis or hemianopia could not be shown. Routine hematological and biochemical test showed no abnormal values. The CSF, obtained by lumbar puncture, disclosed no abnormalities (lactate and pyruvate concentrations were not measured). An EEG disclosed severe hypofrontal disturbances over the left hemisphere and CT showed a hypodensity in the left temporo-occipital area. Angiography of the carotid and vertebral-brobasilar system was without abnormalities. Her neurological condition improved and she continued school activities. Some months later, however, she was readmitted, again with headaches, vomiting, and a confusional state without neurological deficits or other accompanying psychotic symptoms. This time body temperature was raised (38.9°C) without any sign of meningism. There was no leucocytosis, but the erythrocyte sedimentation rate was increased. There were no abnormal laboratory investigations. In 12% of patients, laboratory investigations. In 12% of patients, abnormalities (lactate and pyruvate concentrations were not measured). An EEG disclosed severe hypofrontal disturbances over the left hemisphere and CT showed a hypodensity in the left temporo-occipital area. Angiography of the carotid and vertebral-brobasilar system was without abnormalities. Her neurological condition improved and she continued school activities. Some months later, however, she was readmitted, again with headaches, vomiting, and a confusional state without neurological deficits or other accompanying psychotic symptoms. This time body temperature was raised (38.9°C) without any sign of meningism. There was no leucocytosis, but the erythrocyte sedimentation rate was increased. There were no abnormal laboratory investigations. In 12% of patients, abnormalities were found for the first time and the patient was treated consequently with phenytion. About 4 years later, she was referred to our hospital because of persistent temper tantrums and paranoid ideation. Psychiatric examination disclosed predominantly symptoms of behavioural disinhibition without the presence of clear psychopathology except vague ideas of refer- ence. During subsequent years, the patient developed several depressive episodes, characterised by behaviours, complete retrocerebral deafness, progressive aphasia and apraxia, bradyphrenia, and an increase in focal temporal epileptic seizures and absences, despite maintenance therapy with phenytion, necessitating addition of vigitabrine. She also showed manifest symptoms of muscle weakness. In addition, fluctuating psychiatric symptoms occurred, in particular paranoid delusions, affective instability, and disturbed impulse control with aggressive incidents, for which treatment with haloperidol in dosages varying between 10 and 20 mg daily was given chronically.

At the age of 27, she was referred for diagnostic re-evaluation to the Department of Psychiatry of the University Hospital Dijkzigt in Rotterdam. Ragged red fibres were found by muscle biopsy (Professor HFM Busch, neuropathologist), suggestive of a mitochondrial disorder. Subsequent analysis showed a point mutation 3243 A-G in the muscle biopsy with a mdna mutation percentage of 60 (Dr BA van Oost, University Hospital, Nijmegen) that was compatible therefore with the clinical diagnosis of MELAS. At that time symptomatic treatment with riboflavin and vitamin B complex was started.

Over subsequent years, her condition deteriorated both physically and psychiatrically. The psychiatric picture was characterised by psychotic episodes, including delusions of reference and influence, paranoid ideation, and auditory hallucinations, and sometimes suicidal behaviour necessitating a closed ward. At the age of 31, she was unexpectedly found dead, probably because of acute heart failure.

Postmortem examination of the CNS disclosed pseudolaminar cortical necrosis in the occipital region with many so-called fossilised neurons as well as a partial gliosis with a gliotic but non-broken molecular layer (Dr PTWesseling, neuropathologist, University Hospital, Nijmegen). These abnormalities were found particularly in the superficial parts and not, as in classical cases, in depths of the gyri. The neostriatum, pallidus, and thalamus were normal. The optic tract was somewhat pale and gliotic. The lateral geniculate body, the optic radiation, and the striate area were not or almost not affected.

This report describes a young female patient in whom, after a psychiatric and neurological history of almost 10 years, the diagnosis of MELAS was established by showing ragged red fibres and a point mutation 3243 A-G in muscle biopsy.

Somatic, neurological, and biochemical abnormalities as described in this case, such as incidents of stroke-like symptoms, retrocerebral deafness, disturbances of consciousness, focal epileptic seizures, cognitive deterioration, and increases of lactate and pyruvate in both serum and CSF, are in agreement with those reported by other investigators.7 So far, only one report in the literature could be found describing additional psychiatric symptomatology such as schizophrenia-like symptoms,8 that were present also in this particular patient, especially delusions of reference and influence, auditory hallucinations, and paranoid ideation.

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Letters

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Concerning the pathophysiology of the schizophrenic-like disorder in this patient, it cannot be excluded that the site and laterality of the lesion were involved, as it has been shown in epileptic patients that left side temporal lobe foci increase substantially the risk for the development of a schizophrenic-like psychosis.\(^1\)\(^2\) Moreover, traumatic or ischemic hemispheric lesions may be associated with psychotic episodes.\(^3\) Thus a direct relation between MELAS and schizophrenic-like psychosis is questionable as both the epileptic disorder and the vascular pathology are known to provoke vulnerability to neuropsychiatric morbidity.

The reasons for the delay in establishing the correct diagnosis are most probably not only lack of familiarity with this disorder, but also the complex symptomatology with both neurological, cognitive, and psychiatric features. Moreover, no systematic integrative diagnostic assessment was performed trying to relate objective neurovascular and biochemical abnormalities with behavioural disturbances.

We conclude that in patients with complex and intermittent or progressive mixed neurological and psychiatric disorders, the diagnostic possibility of mitochondrial encephalomyopathy should be considered.

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Primary granulomatous hypophysitis not responsive to pulsed high dose prednisolone therapy: case report

About 30 cases of primary granulomatous hypophysitis have been reported, one third of them being asymptomatic in terms of sellar disease.\(^1\)\(^2\) The aetiology is not understood. The adenohypophysis alone or the whole pituitary gland may be involved.\(^3\)\(^4\) Clinical manifestation of primary granulomatous hypophysitis comprises hypopituitarism and local mass effect. In no symptomatic case reported so far, was the diagnosis suspected before surgery. There is also no experience on preoperative anti-inflammatory high dose corticosteroid therapy for primary granulomatous hypophysitis (PGH).

An otherwise healthy 16 year old girl presented with harmonic dwarfism (body length 1.34 m, body weight 31 kg), pubertas tarda (stage B2P2), and longstanding diabetes insipidus. Dynamic assessment of the adenohypophysis by a combined releasing hormone test and insulin induced hypoglycaemia disclosed somatotrophin and gonadotrophin insufficiency (baseline GHG 2.0 µIU/l, stimulated 1.8 µIU/l, IGF-I 263 µg/l, oestradiol 15 µg/l; baseline LH 0.5 UI, stimulated 0.6 UI; baseline FSH 2.1 UI, stimulated 2.4 UI)). Central diabetes insipidus was confirmed by increased amounts of urinary excretion (range 2.60–3.85 l/day), low specific urinary densities (< 1005), and increased serum natraemia (range 152–155 E/l) and osmolality (range 316–319 osmol/l).

Other laboratory examinations and chest radiography showed no abnormality (in particular no tuberculous, sarcoidosis, or syphilis). MRI disclosed an atrophic pituitary gland and a grossly enlarged pituitary stalk (figure). The presumed diagnosis was longstanding primary hypophysitis.

Pulsed high dose prednisolone therapy was started with 120 mg/day for four days, then tapered by halving the dose every second week during the next seven weeks. Eight weeks after the start of therapy, repeated...
endocrinological and MRI evaluation failed to disclose any improvement. Because other diseases could not be definitively ruled out, biopsy of the pituitary stalk through a subfrontal approach was performed. At surgery, the pituitary stalk was thickened but otherwise of normal appearance.

Histology established the diagnosis of PGH with abundant fibrosis. The presence of microorganisms was ruled out by Ziehl-Nielson and periodic acid-Schiff stains.

The endocrinological and neuroradiological findings did not change during a follow up of 1.5 years.

Primary or idiopathic granulomatous hypophysitis has so far been diagnosed by exclusion: the histological criteria have to be fulfilled and any causative agents of granulomatous or other inflammatory disease and tumorous process have to be ruled out. 1,2,3

Its clinical, endocrinological, and neuroradiological features make primary granulomatous hypophysitis indistinguishable from lymphocytic hypophysitis and often hardly distinguishable from secondary granulomatous hypophysitis due to tumorous sellar processes such as pituitary adenoma, Rathke’s cleft cyst, and histiocytosis X. 1,2,4

Secondary granulomatous hypophysitis due to tuberculosis, syphilis, sarcoidosis, and other inflammatory disease can be ruled out to tuberculosis, syphilis, sarcoidosis, and other inflammatory disease. Two conditions have to be fulfilled. Firstly, primary granulomatous hypophysitis has to be suspected from the diagnostic evaluation. Diagnostic hints are a disproportionate severe adenohypophysial dysfunction compared with the pituitary mass, 5 diabetes insipidus suggesting neurohypophysial involvement, 6 (present case) a usually moderate sellar mass also involving the pituitary stalk, which is homogeneously and markedly contrast enhanced on T1 weighted MRI and hyperintense on T2 weighted MRI, 7 (present case) and the absence of any identifiable causative agent such as inflammatory disease or tumour. 8 Secondly, the suspected primary granulomatous hypophysitis should not cause any pronounced or progressive neurological deficits. None of the above criteria are diagnostic for primary granulomatous hypophysitis and can only suggest it; some uncertainty will always remain. Therefore, during high dose corticosteroid treatment of suspected primary granulomatous hypophysitis, meticulous clinical, endocrinological, and neuroradiological monitoring has to be ensured. In cases that do not fulfill the above mentioned conditions, trans-sphenoidal or, seldom, transcranial surgery, is the therapy of choice. Removal of the usually solid inflammatory process leads to rapid relief of neurological deficits and guarantees accurate histodiagnostic diagnosis. However, improvement of endocrinological deficits is uncommon. 9

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Intracranial venous and dural sinus thrombosis due to protein S deficiency in a patient with AIDS

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