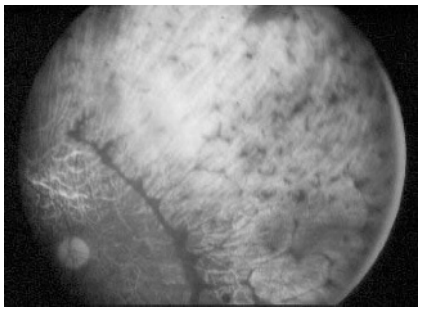

Figure 1 Fundoscopy of gyrate atrophy.

treatment with daily oral pyridoxine was started and a low arginin diet ensured.

Discussion

Two genetic autosomal recessive disorders result from hyperornithinaemia: hyperornithinaemia–hyperammonaemia–homocitrullinuria syndrome, and GA of the choroid and retina with hyperornithinaemia. GA of the choroid and retina is a rare disease, first reported in the Finnish population, but now described all over the world.[1]

The main clinical feature of hyperornithinaemia is its ocular abnormalities. First symptoms are non-specific and appear during the second or third decade, consisting of hesperanopia, myopia and constricted visual field. Fundoscopy generally reveals a bilateral typical pattern of festooned chorioretinal atrophy, initially occurring in the midperiphery, and posterior subcapsular cataract.[2] If not treated, this condition can lead to blindness between the ages of 40–55 years.

Plasma and urinary ornithine levels, mesured by chromatography, are constantly raised (5–20 N).

Ornithine is an amino acid that plays a role in the metabolism of urea, creatine and polyamines and that can be consumed during a reaction catalysed by the OAT in the mitochondria.

Hyperornithinaemia is caused by OAT deficiency secondary to OAT gene mutation. More than 50 pathogenic mutations of the OAT gene, mapped in 10q26, have already been detected.[3] Eighty-five per cent of patients with gyrate atrophy have a normal amount of normal-sized OAT mRNA, but only 10% have normal amounts of normal-sized OAT protein. This finding suggests a normal transcription but abnormal transduction.

Systemic involvement, such as thin and rare hairs, mental retardation with diffuse brain atrophy, slow background electro-encephalographic abnormalities and muscular weakness, has been described previously in association with GA.[4] Muscular histological examination, even in patients without weakness, can show muscular abnormalities such as type II fibre atrophy and sarcoplasmic tubular aggregates. The pathogenic role of tubular aggregates is unknown and uncertain. These distinctive inclusions are not specific and have been described in normal subjects, in some other muscular diseases, such as acromegaly, and in porphyria cutanea tarda.

An arginine-restricted diet can reduce plasma ornithine levels and completely prevent retinal degeneration, over a 12-month period, in a mouse model of OAT deficiency.[5] Long-term reduction of ornithine levels by the arginine-restricted diet has been proposed in patients with GA; progression of chorioretinal lesions can be slowed if the diet is started at an early age.[6]

Administration of pyridoxine stimulates residual OAT activity and is associated with a significant reduction in ornithine plasma levels in some genetically determined responsive patients. The daily dose of pyridoxine is still under discussion (between 20 and 600 mg). However, the pyridoxine therapy does not stop the progression of chorioretinal degeneration.

Conclusion

GA with hyperornithinaemia is a metabolically inherited disease and is one of the rare causes of both ocular and muscular involvement. Lack of specificity of initial ophthalmological symptoms can be responsible for a misdiagnosis. When muscular symptoms are associated with these ophthalmological signs, the diagnosis of GA of the choroid and retina due to hyperornithinaemia has to be considered and ornithine plasma levels have to be assayed.

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Stiff person syndrome (SPS), a basal ganglia disease? Striatal MRI lesions in a patient with SPS

Stiff person syndrome (SPS) is characterised by muscle rigidity and episodic spasms involving the axial and limb musculature. The hallmark is co-contraction of agonist and antagonist muscles, with continuous motor unit firing at rest. An autoimmune pathogenesis is based on the presence of anti-glutamic acid decarboxylase antibodies (anti-GAD, rate-limiting enzyme to synthesise γ-aminobutyric acid (GABA), in presynaptic GABAergic inhibitory synapses), and association with other autoimmune disorders and autoantibodies, and on response to immunotherapy. There is only a limited number of cases with brain MRI abnormalities. Our patient is the first reported case of SPS with MRI striatal abnormalities.

Case report

A 69-year-old woman came in for consultation with an 18-month history of back pain, stiffness and progressive difficulty at walking. She had developed asymmetrical rigidity in her legs, with the left one being worse, from falls. In one of these falls she broke her left humerus. That limb remains useless, painful and rigid. She had progressive difficulty in turning over in bed and in getting up. In stressful situations and when trying to move, she had painful spasms in the left leg starting distally with toe and ankle extension, and progressing to knee and hip flexion while raising the leg from the bed. She became progressively bedridden. Her medical history was notable for diabetes mellitus (controlled with acarbose) and hypertension (controlled without drugs). A neurological examination showed stiffness and limitation in the range of active and passive movements in the left leg, left arm and, less pronouncedly, in the right leg. Also, there was slowing of finger, hand and arm movements in the left hand. She found it difficult to raise her left leg, which sometimes developed into painful spasms. She had decreased facial expression, cogwheel rigidity in both superior extremities and stony lumbar rigidity. Plantar reflexes were flexor and deep tendon reflexes were symmetrically brisk. She needed help to sit down and was afraid to walk even with aid. On the other hand, her mental status, speech and cranial nerves were normal.

The results of blood tests, including antinuclear antibody, endomysial, gliadin, transglutaminase, mitochondrial, smooth muscle, parietal, anti-LKM1 (autoimmune hepatitis), thyroid peroxidase and thyroglobulin, were negative. Levels of folic acid, vitamin B_{12}, T4, thyroid-stimulating hormone, rheumatoid factor, C-reactive protein, anti-streptolysin O, immunoglobulins and complement were normal. Serum anti-GAD level was 14 000 U/ml (radioimmunoassay). Also, the patient tested negative for anti-Yo, anti-Hu, anti-Ri and antiampiphysin. Serum anti-GAD increased to 60 400 U/ml (N<1 U/ml).

The patient rejected lumbar puncture. Nerve conduction was normal and electromyography showed normal motor unit potentials, an inability to relax any of the muscles tested, and continuous motor unit activity.

Cervical and lumbar MRI was normal. Cerebral MRI showed bright hyperintense changes on fluid-attenuated inversion recovery (FLAIR) and T2 in both striatal regions (more intense in the right striatum corresponding to

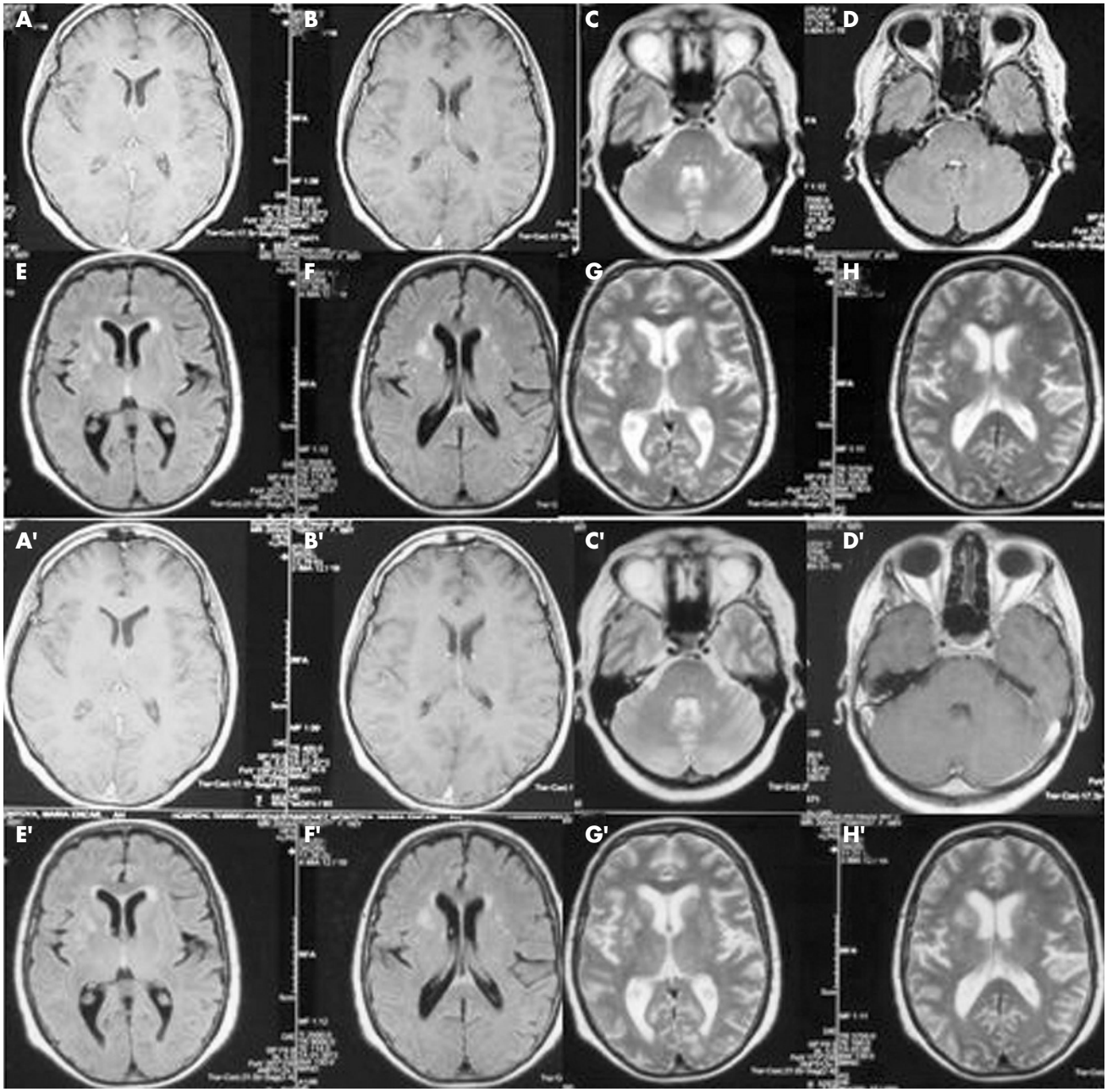

Figure 1 (A,B) Normal post-gadolinium T1. (C) Left middle cerebellar peduncle T2 lesion, (D) enhancing T1. (E–H) Bilateral striatal hyperintense lesions (right predominant) in fluid-attenuated inversion recovery (E, F) and T2 (G,H). (A′–H′) MRI after 6 months. The only clear difference is absence of enhancement in the left middle cerebellar peduncle post-gadolinium T1 (D′).

the more symptomatic left side), and a lesion in the left middle cerebellar peduncle on T2, the only one enhancing with gadolinium (fig 1). Treatment was started with L-dopa without improvement. The patient improved after diazepam (25 mg/day) and a 5-day course of intravenous immunoglobulin (0.4 mg/kg/day). Spasms and pain disappeared, and she was able to walk without aid after discharge (12 days in hospital). After 6 months, MRI was similar, and on follow-up her gait was slow but independent. Spasms, rigidity and pain on the legs disappeared. Rigidity and limitation to abduct the left shoulder and to extend the left elbow persisted, and hence another 5-day course of intravenous immunoglobulin was infused. After 2 weeks, she reported improvement in walking and less rigidity on the left shoulder.

Discussion

The absence of structural MRI changes in most cases suggests that SPS is a functional rather than a structural disorder. However, here are some MRI findings in patients with SPS.

- Cranial T2 MRI hyperintensity in the temporal lobes, hypothalamus and pons in a 71-year-old patient with paraneoplastic SPS (amphiphysin+, anti-GAD−), opsoclonus and encephalopathy.[1]
- Spinal T2 hyperintense lesion (C2–C7) in a patient with SPS with lymphocytic pleocytosis of the cerebrospinal fluid (CSF) and oligoclonal bands. Amphiphysin autoantibodies were detected in serum and CSF. No malignancy occurred during a 3-year period.[2]
- Atrophy and hyperintense T2 left hippocampus in a 22-year-old woman with SPS and seizures.[3]
- Bright signal on FLAIR in the right hippocampus in a 12-year-old boy with SPS anti-GAD+ and a 3-year history of type 1 diabetes.[4]
- T1-weighted midline cerebellar atrophy in a 38-year-old woman with anti-GAD+ SPS

and eye movement abnormalities without evidence of myasthenia over 12 years.[5]

There are a few postmortem studies. The relevant findings are: in anti-GAD+ SPS, reduction of small spinal neurons and changes in larger alpha-motor neurons, as well as selective depletion of Purkinje cells (GAD-containing neurones), have taken place; in paraneoplastic SPS (anti-GAD−, amphiphysin positive), brainstem encephalitis has led to lymphocytic infiltrates, neuronal loss, gliosis and perivascular lymphocytic cuffs.

The pathogenic role of anti-GAD is controversial. Up to 65% of SPS cases have anti-GAD, but in paraneoplastic SPS, associated with antibodies to amphiphysin and gephyrin, anti-GAD are rarely present. Although uncommon, anti-GAD have been reported in other neurological diseases such as cerebellar ataxia, drug-resistant epilepsy, tremor of the mouth floor and periodic alternating nystagmus. Anti-GAD have also been found in diabetes and other autoimmune diseases in a lesser proportion.

In vitro, anti-GAD inhibit GAD activity; however, in vivo it is uncertain (antibodies circulate extracellularly, but GAD is intracellular).

In SPS, the concentration of GABA is reduced in CSF and assessed by magnetic resonance spectroscopy; GABA is decreased in the sensorimotor cortex. GABA is the major inhibitory neurotransmitter in the striatum and GAD activity was detected in spiny and non-spiny striatal neurons. Medium spiny projection neurons comprise 90–95% of the striatal neuronal population and are inhibitory via GABA. The basal ganglia inhibit undesirable or competing movements and postural synergies initiated by cerebral cortical mechanisms, with help from the cerebellum.

GABA levels are decreased in the contralateral sensorimotor cortex and lentiform nuclei in focal hand dystonia. In Huntington's disease, striatal neuronal dysfunction would produce an inability to inhibit unwanted movements, resulting in chorea. In our patient with SPS, striatal neuronal dysfunction might have produced inability to inhibit simultaneous co-contraction of agonist and antagonist muscles. Either functional or structural striatal abnormalities may play a role in SPS, but more studies are needed to confirm this hypothesis.

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Möbius syndrome in association with the REM sleep behaviour disorder

We report a 34-year-old woman with Möbius syndrome in association with lifelong sleep disturbance diagnosed as rapid eye movement (REM) sleep behaviour disorder (RBD). RBD proved treatment resistant and the possible structural reasons for this are discussed.

Case history

The patient was a 34-year-old woman who was noted at birth to have bilateral abducens nerve palsy, complete facial diplegia, club feet, malformation of the right upper limb and chest wall with an underdeveloped right hand and an absent pectoralis major. These abnormalities were non-progressive and a diagnosis of Möbius syndrome was made based on the characteristic clinical features. The Poland anomaly (pectoralis major hypoplasia and mammary hypoplasia) is associated with 13% of cases of Möbius syndrome.[1]

From birth, the patient's mother noted sleep disturbance with brief crying and vocalisation as well as twitching arm and leg movements during sleep. The sleep disturbance became more marked over time and by the age of 3 years until the current day she has suffered episodes of screaming and abnormal movements occurring in the second half of the night on a nightly basis, usually between 02:00 and 04:00. Her mother described screaming with non-stereotyped, flailing movements of her arms and legs lasting several minutes. The patient's legs often moved as if running in the bed. She had injured both herself and her mother when restrained during an attack and was initially confused after being woken.

The history from the patient was of persistent unpleasant dreams, with recurring themes. Examples included being chased through rooms with a gun and being hunted by guards in a concentration camp. The dreams did not change in a different environment but increased during menstruation and stressful life events.

There was no other past medical history; in particular there was no history of snoring, restless legs syndrome or sleepwalking. There was no family history of any psychiatric or sleep disorder. She was a teetotal non-smoker.

Investigations

A diagnosis of RBD was made on the basis of her clinical description and she was investigated at Papworth Hospital. MRI of her brain with axial T1 weighted, T2 weighted and fluid attenuated inversion recovery sequences were normal, with no pontine abnormality seen. Routine 12 lead EEG while waking and drowsy was normal.

She underwent polysomnography on two consecutive nights using a standard protocol including video recording, sleep EEG (leads C3-A2, O1-A2), electrooculogram, and submental and bilateral anterior tibialis electromyography (EMG). Respiratory effort, airflow and oxygen saturation were measured to exclude sleep apnoea syndrome. Sleep stages were scored according to standard criteria in 30 s epochs. Sleep latency, sleep efficiency and percentage of stage 1, stage 2, stage 3, stage 4 and REM to total sleep time were recorded.

There was no sleep disordered breathing or periodic leg movements of sleep. REM sleep was difficult to stage because the facial diplegia and opthalmoplegia affected interpretation of the submental EMG and electrooculogram. Her sleep stages corresponded to 90 min cycles with clearly defined slow wave sleep and at 02:15 and 04:30 on the second night during non-slow wave sleep she had brief episodes with vocalisation and some flailing movements of her right arm (fig 1).

Treatment

The patient tried numerous medications sequentially over many years without benefit. In order, clonazepam, melatonin, carbamazepine, sertraline and temazepam were used at therapeutic doses, each for at least 3 months. None of the medications decreased the disturbing dreams. Cognitive behavioural therapy was also unsuccessful.

Discussion

Möbius syndrome was initially defined as congenital facial diplegia and bilateral abducens nerve palsies. The description has since been broadened as many patients have other cranial nerve palsies, with variable opthalmoplegia, bulbar dysfunction and tongue atrophy all seen. Musculoskeletal abnormalities occur in one third of patients with clubfeet, the commonest deformity, but brachydactly, arthrogryposis and the Poland anomaly are also seen.[1]

The pathogenesis of Möbius syndrome has been debated but simultaneous limb malformations with cranial nerve dysfunction suggest disruption of normal morphogenesis during a critical period in the development of the embryonic structures of these regions. In a review of 37 patients with Möbius syndrome, the authors concluded that the widespread involvement of various motor nuclei and axons made it more likely to be a syndrome of rhombencephalic maldevelopment, rather than an isolated cranial nerve or nuclear developmental disorder.[1] Imaging studies showing a variety of brainstem anomalies, including absence of the facial nerve, support this theory.[1]

Typical idiopathic RBD affects elderly males, often in association with neurodegenerative diseases such as Parkinson's disease and dementia with Lewy bodies. Animal studies indicate that the pedunculopontine region of the upper brainstem is involved. RBD is usually well treated with clonazepam.[2]

It is possibly surprising that a disorder that causes brainstem abnormalities does not produce abnormalities of REM sleep more frequently. None of a large cohort of patients enrolled into a specialist Möbius clinic complained of disturbing dreams (Padberg GW, personal communication, 2006). Sleep disturbance in Möbius syndrome has been reported in association with both central and obstructive sleep apnoea and thought to be secondary to palatal dysfunction.[1] There are no individual reports of RBD in association with this condition in the literature although there are reports