Dystonia, tremor, and parkinsonism in a 54 year old man with 2-hydroxyglutaric aciduria

Glutaric aciduria is often considered to be a rapidly progressing dementing illness with only occasional extrapyramidal symptoms, usually described as dystonia. We present a case of late onset 2-hydroxyglutaric aciduria and slowly progressive dystonia and parkinsonism.

Case report
A 54 year old man was referred to the University of Florida movement disorders center for management of "end stage Parkinson's disease". He was diagnosed with developmental delay and mild cerebral palsy by his paediatrician, for a failure to meet motor milestones. He had below average grades in school and graduated high school two years behind his age matched peers. At age 26, he noticed a mild intention tremor in his right hand, a mild head tremor, and mild unsteadiness in walking. These were assumed to be potentially parkinsonian features, and later in his 30s he was given the assumed diagnosis of Parkinson's disease. He was treated with levodopa, dopamine agonists, a monoamine oxidase inhibitor, and anticholinergics, which all failed to help his symptoms. He was gainfully employed by the center for management of "end stage Parkinson's disease''. He was diagnosed with mildest postural tremor. Power, reflexes, and sensory examination were normal. On cerebellar examination he was alert and oriented to person and place. His memory was tested (3/3 registration and 1/3 recall after five minutes). He had a hypophonic dysarthria with palliilalia. Gerstmann features (right/left confusion, finger anomaly, acalculia, and agraphia) were all impaired. He had frontal release signs including a root, snout, and glabellar tap. He had frontal lobe impairment including problems with Luria 2 and 3 step command testing, anti-saccade testing, problems with crossed response inhibition, and motor impersistence. Stereognosis and graphesthesia were intact. Cranial nerve examination revealed only saccadic pursuit. He had a tongue tremor. Power, reflexes, and sensory examination were normal. On cerebellar examination he was hypermetric on finger to nose testing, with past pointing and ataxia.

Movement disorder examination revealed prominent parkinsonian features including rigidity, bradykinesia, shuffling gait, and balance problems. His hands were mildly dystonic. He had mild bilateral postural intention tremors. His posture was stooped and he had decreased arm swing and shuffling steps. He retropulsed on a pull test and could not perform tandem gait. In addition, he had a masked face, pallilalia, and severe micrographia. His off medication Unified Parkinson's Disease motor scale (UPDRS) examination was 55. After taking his usual medications (trihexyphenidyl and selegiline) he was re-examined one hour later and his UPDRS score was unchanged (55). He had more dystonia in his hands while on his medications.

His previous diagnostic evaluation included a serum lactic acid, which had revealed a normal thyroid stimulating hormone concentration, normal liver function tests, normal ammonia concentration, and normal reactive plasma reagent. Head magnetic resonance imaging had been performed one year before presentation and the flair images revealed prominent white matter hyperintensities in the frontal and parietal regions, with posterior ex vacuo dilatation of his lateral ventricles (Figure 1), and mild cerebellar atrophy. Urine organic acids were sent and revealed 2-hydroxyglutaric aciduria.

Discussion
This case demonstrates that older patients with parkinsonism may have inborn errors of metabolism. Our patient was unique in that until his mid-20s and later when he lost his job in his mid-30s, he was assumed to have mild cerebral palsy, and only after developing other parkinsonian features was he later misdiagnosed as having Parkinson's disease. The important clinical feature that shocked us in this patient were the developmental delay, the progression of symptoms leading to a mental incapacity to hold his job, and the parkinsonian features that were unresponsive to levodopa and other agents. In addition, an MRI, which was carried with him to the appointment, had changes indicative of glutaric aciduria. A differential diagnosis in this case should have included other non-levodopa responsive disorders that can present with movement disorders, such as propionic acidemia, methylmalonic aciduria, glutaric aciduria, and leucodystrophy. Given his relatively benign course, he probably has L-2-hydroxyglutaric aciduria and not D-2-hydroxyglutaric aciduria. Our patient unfortunately died as a result of an accident shortly after his evaluation, making confirmation of the L isofrom impossible.

2-Hydroxyglutaric aciduria is a rare inborn error of metabolism that was first recognised in the L isofrom by Duran and colleagues and later defined clinically by Barth et al. There is less known about the molecular biology and underlying biochemical defect than in other amino acidurias. Further cases have been identified and have detailed clinical, biochemical, radiological, and pathological characteristics that have established a spectrum of the disease. Several subtypes have been identified and hydroxyglutaric aciduria has been proposed to have an autosomal recessive inheritance, occurring in both D and L isofroms. Most of the cases reported in the literature are identified in early childhood. The D isofrom usually presents with neonatal or early infantile encephalopathy, seizures, extrapyramidal symptoms, and cardiomyopathy. In contrast, the L isofrom may present within the 1st years of life with non-specific motor delay, and later cognitive and motor developmental delay. Gait ataxia may occur as early as the 2nd year. Additional findings include occasional pyramidal and extrapyramidal features and dystonia, with a pre-dilection for the hands. Progressive mental retardation is common in these patients. Most cases are diagnosed in childhood but Clerc et al. in 2000, reported an adult patient with tremor and excessive urinary excretion of L-2-hydroxyglutaric aciduria. Our case also highlights the possibility of this disorder presenting later in life with dystonia, tremor, and parkinsonism.

Imaging and urine samples are very helpful in making this diagnosis. Neuroimaging findings in L-2-hydroxyglutaric aciduria reveal subcortical leuencephalopathy (as seen in our case), and may also show atrophy of the cerebellum. Larnaout and colleagues performed a necropsy on a patient with childhood onset of cognitive and motor delay and epilepsy whose brother was diagnosed with L-2-hydroxyglutaric aciduria and they described the diffuse white matter changes as demyelination with spongiform, cavitating cystic lesions and cerebellar white matter gliosis. This pattern of involvement was consistent with the MRI results and was considered to be the typical spongiosis encountered in disorders of amino acid metabolism.

The diagnosis of hydroxyglutaric aciduria is made by analysing urine samples with gas chromatography. The L isofrom reveals a solitary peak of 2-hydroxyglutaric acid, whereas the D isofrom may have other citric acid cycle intermediates present in addition to D-2-hydroxyglutaric acid. In the USA, testing is available for the urinary detection of 2-hydroxyglutaric acid, but unfortunately American laboratories are unable to distinguish between the L and the D isofrom.

This case reminds us that inborn errors of metabolism can be a cause of parkinsonism, and in selected cases an investigation should...
be performed with urine organic acids so that this diagnosis can be quickly made. With the emergence of new genetic therapies for biochemical diseases it may be important in the future to make this diagnosis early in the course of the disease.

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Transient myasthenia gravis in an elderly woman
Myasthenia gravis is usually a chronic disorder, although remission rates of 25–30% can be expected with judicious interventions such as thymectomy and immunosuppression in appropriate cases. Spontaneous remission is rarely observed. Oosterhuis found a remission rate of only 1% per annum over 17 years among 180 patients with generalised myasthenia gravis treated with anticholinesterases alone.1 We describe a case of ocular and bulbar myasthenia in which there was complete recovery over a matter of weeks without immunosuppressive agents. The patient, a 78 year old woman, developed acute, painless left sided ptosis in October 1998 while on holiday abroad. There was no diplopia. She had developed hypothyroidism one year before but was euthyroid on replacement therapy. The ptosis resolved gradually over the next few days. There was no family history of autoimmune diseases. Two weeks later she found she could not chew properly towards the end of a meal. The jaw weakness recovered the following week and was almost complete by the time she had to support her jaw while talking and eating. She had slight dysphagia but there was no history of choking, breathing problems, or limb weakness.

On examination in January 2003, there was no diplopia. She was alert and well orientated, with a body mass index of 22. She had no other significant medical problems. Her medical history consisted of hypothyroidism, for which she was being treated with levothyroxine tablets. She had been diagnosed with myasthenia gravis in 1982 at the age of 21 years. Pyridostigmine was gradually withdrawn and she had normal acetylcholine receptor (AchR-abs) titres at 11 nmol/l. She was euthyroid on replacement therapy. The ptosis was normal although her AchR-abs remained strongly positive at 11 nmol/l. Her thyroid function tests were normal. She was given pyridostigmine 60 mg twice daily, which improved her ocular symptoms. She had normal acetylcholine receptor antibodies (AchR-abs) at 11 nmol/l (normal range 0 to 0.25 nmol/l). Other autoantibodies were negative apart from a positive gastric parietal cell antibody. Computed tomography of the mediastinum did not show any thymic abnormality. She was given pyridostigmine 60 mg twice daily, and her symptoms gradually improved. On repeat assessment one month later, there was no evidence of ptosis and the jaw weakness seemed to be improving, though she still needed to hold her jaw when speaking for a few minutes. Repetitive nerve stimulation of left frontalis and obicularis oculi showed no decremental response. Electromyographic examination of the right biceps, extensor digitorum communis, and left frontals muscles was also normal.

In view of the improving symptoms and the electrophysiological findings, it was decided to continue pyridostigmine alone and steroid treatment was not initiated. Her symptoms continued to improve. By April 2003, she was completely asymptomatic. The pyridostigmine was gradually withdrawn over one month. She remained asymptomatic on follow up in September 2003. Neurological examination was entirely normal although her AchR-abs remained positive at 5.00 nmol/l.

COMMENT
To our knowledge, transient myasthenia gravis has not been described previously in a patient of this age. It is known to occur in 10–15% of infants born to mothers with myasthenia as a result of transplacental transfer of maternal antibodies, and there is a report of transient myasthenia in autimmune disease resulting from HIV infection.3 In that study, seven HIV infected patients presented with transient myasthenic symptoms. Four of them had positive AchR-abs. In one, myasthenia gravis and coincident autoimmune thrombocytopenia both resolved following anti-retroviral treatment. Our patient had no history of preceding infection, although there was a history of thyroid disease.

The persistence of high levels of AchR-abs despite clinical resolution is of interest. There is no direct correlation between antibody titre and clinical state in individual myasthenic patients.4 The resolution of clinical symptoms and signs, despite persistent acetylcholine receptor antibodies, presumably reflects a positive balance of acetylcholine receptor genesis to antibody mediated destruction. Late onset myasthenia gravis differs from the typical form in several ways. The HLA DR3 haplotype is uncommon in late onset disease, while thymomas are more common. It is said that late onset disease is more severe and less likely to remit, and that bulbar involvement is more common.5 Response to conventional treatment is also less satisfactory than in the typical form. Our patient was therefore atypical of this older group.

A recent cohort study suggested that myasthenia gravis might be underdiagnosed in older people.6 In that study, 2000 asymptomatic individuals aged 60 and over, who participated in the Oxford healthy ager project, were screened for AchR-ags. Surprisingly, 0.71% were seropositive. Four of eight seropositive subjects had a diagnosis of “stroke” or “transient ischaemic attacks” and the authors concluded that these patients might have been misdiagnosed. It is therefore possible that myasthenia gravis in the elderly is sometimes missed and that the clinical course may in some cases be more benign than appreciated.

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“Doctor, I can hear my eyes”
report of two cases with different mechanisms
An unusual but fascinating symptom is the one described by patients complaining that they can hear their own eye movements. We report two cases, with different postulated mechanisms.

Case reports
Patient 1
A 53 year old woman presented with a tendency to fall to the left. She did not experience hearing difficulties or tinnitus. Clinical examination was unremarkable other than increased sway on Romberberg. Pure tone audiometry was normal other than bilaterally mildly elevated thresholds of 30 dBHL at 8 kHz. However left sided ipsi- and contra-lateral stapedial reflexes were elevated, and auditory brain-stem evoked responses, while normal on the right, showed increased latency of wave V on the left. Serial MRI scans demonstrated an enlarging left vestibular schwannoma. Trans-labyrinthine resection of the tumour was complicated by a left cerebellar infarct and hydrocephalus, and subsequently the patient continued to experience imbalance. Two years post-operatively, direct questioning about tinnitus led to the patient describing tonal tinnitus in the left ear on looking to the left, in which up-gaze increased the pitch, while down-gaze lowered the pitch. Notably she said “I feel I could play a tune with my eyes”.

Patient 2
A 32 year old man presented with visual instability and a tendency to fall forward and to the left provoked by loud sounds such as
the telephone ringing in his left ear. His auditory symptoms included being able to hear his heart beats, bone taps, and footsteps. Additionally he complained of a soft low pitched sound in his left ear “rather like moving a hard-pressed finger across a clean, wet china dinner plate” when he moved his eyes. These symptoms could be reduced if the patient tensed his abdominal muscles. Pure tone audiometry showed normal air conduction hearing thresholds bilaterally other than a mild elevation of 35 dBHL at 0.25 kHz on the left. Bone conduction hearing levels were normal, perhaps even supra-normal, with thresholds of −10 dBHL at 0.5 and 1 kHz bilaterally, giving rise to an “air-bone gap” at these frequencies. Clinical examination and three-dimensional video ocolography demonstrated left beating torsional nystagmus provoked by the patient humming, and CT scanning of the petrous temporal bones revealed bilateral dehiscence of the superior semicircular canals (fig 1).

Discussion

Patient 1 has gaze-evoked tinnitus, a phenomenon first described in 1982 that was initially thought to be rare, but subsequently reported to be surprisingly common (prevalence 19–36%) in one study of patients post vestibular schwannoma resection. It has also been described in patients with cerebellopontine angle meningioma, meningeal metastases of malignant melanoma, and sudden sensorineural hearing loss. It may develop months post-operatively, and is usually heard in, and caused by moving the eyes towards, the diseased ear. The exact mechanism is not known, but it has been postulated that neural plasticity mechanisms activated by unilateral deafferentation result in cross-talk between neural elements controlling eye movements and the central auditory system. Indeed, functional imaging studies of patients with gaze-evoked tinnitus have shown anomalous activation of the auditory lateral pons and auditory cortex, enhanced by failure of cross-modality inhibitory mechanisms.

Patient 2 has Tullio phenomenon, a condition in which sound and/or pressure stimulates the vestibular system. These patients often complain of abnormal auditory sensations such as “hearing footsteps vibrating through the body”, and finding the noise of chewing loud enough to make understanding of conversations at mealtimes difficult. Supra-normal bone conduction thresholds, or so-called “conductive hyperacusis”, has been reported in other patients with Tullio phenomenon, and dehiscence of the superior semi-circular canals is thought to be the commonest associated pathology. It is postulated that the dehiscence may act as an alternative lower impedance pathway for sound energy, enabling these patients to hear the movements of their eyeballs within the bony sockets, these sounds being conducted through the skull. It is interesting to note that although our patient had dehiscence of both superior semi-circular canals, he was only symptomatic on the left side. This could be explained by the Tullio phenomenon being multi-fac torial in nature, and additional factors such as trauma or bone remodelling need to be present as well as the dehiscence before the clinical features become manifest.

CASE REPORT

A 52 year old man complained of diploria, dizziness, vertigo, decrease of consciousness, memory impairment, and hyperphagia. These symptoms occurred abruptly while he was painting the gate in his garden.

The diploria and vertigo disappeared in about 15 minutes, while hyperphagia and memory impairment lasted for about 24 hours and completely disappeared the following day on awakening. Instead, amnesia concerning the event is still present.

The decrease of consciousness consisted of slight hypersomnolence (the patient could easily be awakened by auditory and verbal stimulation) and was present only at the onset, while memory impairment was noted only later. The patient’s wife reported that he kept repeating the same questions to her, and was unable to remember where he was or what he was doing. The patient’s main concern was food, and his attention could not be diverted during his meals.

The following day his wife took him to the hospital. Neurological examination on admission revealed only retrograde amnesia about the events that had occurred in the previous 24 hours, along with fatuous behaviour. The medical history was not significant. Cranial computed tomography and extracranial Duplex ultrasonography revealed no abnormalities. Later in the day, brain magnetic resonance imaging (MRI) revealed an ischaemic lesion involving the medial portion of the left thalamus in the territory of the left thalamo-striatal perforating artery (fig 1). MRI-angiography of extracranial and intracranial cerebral arteries was normal.

A transthoracic echocardiogram was normal, while a transoesophageal echocardiogram revealed an atrial septal defect without a patent foramen ovale. Conventional vascular risk factors (hypertension, diabetes, hypercholesterolaemia, and smoking) were absent. Routine laboratory studies including coagulation profiles were normal.

During the hospital admission, the patient’s clinical condition progressively improved and he was discharged eight days later without any neurological symptoms.

Two weeks later he was submitted to a neuropsychological test battery to assess reasoning (Raven PM47), short term memory (verbal and spatial span), learning (paired associate and Corsi spatial learning), attention (visual search), and frontal executive functions (Nelson card sorting test, trial making B, category, and literal fluency). Anxiety and depression were investigated by the state-trait anxiety inventory and the Beck depression inventory. Results were within the normal range (<1 SD) for all the tests.

COMMENT

The anatomical substrates of eating disorders are conventionally the basal ganglia and the cortico-limbic areas. In our patient compulsive hyperphagia was associated with the functional features of medial thalamic ischemia. The patient presented with signs and symptoms of the so called “top of the basilar
other endocrine dysregulations. Characterised by dysregulation of hunger caused by hypothalamic dysfunction are the posteromedial thalamus (PMT), from the posterior cerebral artery and supply infarction. Syndrome’ and of thalamic perforating artery ischaemic lesion involves the medial thalamus (B) in the territory of the thalamo-perforating arteries (3800/120/2). (B) Axial view, T2 weighted (3800/120/2). A Figure 1

In diencephalic lesions hyperphagia may result from hypothalamic, thalamo-cortical, and limbic dysfunction. Lesions involving the ventromedial hypothalamus, the amygdala, and the fibre bundle from the substantia nigra to the basal ganglia alter the signal of satiety and food intake. Eating disorders caused by hypothalamic dysfunction are characterised by dysregulation of hunger and satiety signals and are associated with other endocrine dysregulations.

Cortical lesions may cause eating disorders if they involve the temporal and frontal association areas connected to the basal and diencephalic systems. Moreover, clinical observations and animal studies suggest that the limbic structures and their connections are strongly involved in the regulation of appetite.

In our patient the acute occurrence of compulsive eating was part of a complex behavioural and neuropsychological disturbance typical of medial thalamic dysfunction. Behavioural abnormalities may be more easily explained by bilateral involvement of the medial thalamic region. Indeed an embolic occlusion of the distal portion of the basilar artery may have caused a transient bilateral thalamic ischaemia. The definite infarct involved the left thalamus and was completely asymptomatic.

In our patient we believe that transient thalamo-cortical dysfunction because of impairment of the connection between the medial thalamic nuclei and the frontal or temporal lobes may have been the determinant of the compulsive hyperphagia. This compulsive hyperphagia may be the equivalent of the utilisation behaviour described in bilateral PMT infarction, in which patients automatically and inappropriately handle and use objects placed before them, even though not used by them.

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Case study: cerebrovascular parkinsonism with levodopa addiction

Levodopa (L-dopa), the mainstay of treatment for idiopathic Parkinson’s disease (IPD), has a mild stimulant effect and may cause agitation, restlessness, and euphoria even in normal subjects. It is associated with a well documented withdrawal syndrome consisting of confusion, muscular pain, and rigidity. This can progress to involve symptoms comparable with neuroleptic malignant syndrome, including pyrexia and increased creatine kinase. There is now good evidence that L-dopa is addictive, and there are many case reports of patients with IPD who seek to increase their L-dopa dose to high levels because of psychological dependence rather than therapeutic benefit. The largest series of such patients’ suggested that L-dopa dependence results in paranoia, hypomania, hypersexuality, and euphoria associated with weight loss and severe dyskinesias. Many of the behavioural changes are similar to those seen in amphetamine or cocaine abusers and have been termed “hedonistic homeostatic dysregulation”.

CASE REPORT

An 81 year old woman had been diagnosed with Parkinson’s disease 10 years before. She reported a five year history of extremely frequent but intermittent severe pain and stiffness in all her muscles, resulting in severe disability and distress. Her general practitioner had tried amitriptyline and baclofen with no effect. The only effective treatment was Madopar, a combination of levodopa and benzemerizide hydrochloride, which she took in large doses every two hours. She admitted taking in excess of 2.3 g every 24 hours. She even woke in the night to take Madopar tablets. She was obsessive about her drug regimen and would not allow even minor changes. Her husband said that she was hostile, paranoid, and very demanding. She had never suffered from hallucinations or dyskinesias. Her previous records indicated ongoing problems with weight loss, investigated over several years but with no apparent cause. She had undergone computed tomography of the brain in 2001, which showed multiple white matter lesions secondary to chronic ischaemic damage.

She presented as a cachectic, frail, elderly woman bent over in a wheelchair. She weighed 34 kg. She was unable to stand for walk owing to pain and stiffness. She was slightly confused, with a mini-mental state examination (MMSE) score of 24/30. She appeared to be in constant pain and was uncooperative with examination. Despite this, she had no evidence of tremor, rigidity, or bradykinesia. There were no other significant neurological findings.

She was admitted to hospital for slow supervised withdrawal of her Madopar. Blood tests including blood count, electrolytes, creatine kinase, thyroid function, and inflammatory markers were all in the normal range. She refused further investigation by magnetic resonance imaging or single photon emission computed tomography. She was only able to tolerate a very slow withdrawal of L-dopa owing to severe muscular pain, and it took two separate admissions over five months to complete the withdrawal. It was possible to keep her off L-dopa for a period of four weeks, during which she regained her appetite and weighed 40 kg. She was clear in her mind and her MMSE score was 30/30. She was no longer paranoic and no longer wanted to take L-dopa treatment. She became pain-free. Her
handwriting was large and legible. She was able to walk with a Zimmer-frame, but had a wide based shuffling gait compatible with a diagnosis of small vessel cerebrovascular disease.

Following that period she became depressed and withdrawn. Paroxetine did not help but the reintroduction of Madopar, in a dose of 62.5 mg three times daily, helped to alleviate the depression. After one year of follow up she remained mobile with help. She had not developed tremor, extrapyramidal rigidity, or significant bradykinesia. Her appetite and alertness continued to be good. She refused any further reduction in the dose of L-dopa.

**COMMENT**

Despite its high prevalence, IPD is often a challenging diagnosis. Up to 25% of patients considered to have this condition by a neurologist may have an alternative diagnosis. In the community, the diagnosis may be wrong in nearly 50% of cases. Where there is difficulty in making a diagnosis, a trial of L-dopa is often useful. However, it is possible that L-dopa dependency can occur even in patients without IPD. They can develop withdrawal symptoms of muscular aching and stiffness, which superficially resemble worsening parkinsonism and obviously respond well to L-dopa, giving the impression of a helpful treatment. In our patient’s case, larger and larger doses of L-dopa were prescribed over many years, leading to physical and psychiatric effects compatible with “hedonistic homeostatic dysregulation.” She became profoundly disabled as a result of L-dopa dependence, the manifestations of which were much worse than the symptoms with which she had initially presented.

The psychiatric effects of L-dopa dependence are well documented, including severe depression after withdrawal. However, the characteristic severe muscle pain suffered by our patient has not been reported before. We speculate that long term L-dopa treatment causes changes in the expression of central dopamine receptors such that withdrawal leads to unpleasant symptoms, even in people without Parkinson’s disease. A similar mechanism may underlie the development of “dopaminergic malignant syndrome”.

It is our suspicion that there may be other patients without IPD who are dependent on L-dopa. It is important that L-dopa is not considered a benign medication, and trials of treatment with this agent should be carefully supervised. Any patient taking L-dopa in large doses without dyskinesias should have the diagnosis reconsidered. Any patient with IPD in whom muscular pain is a prominent symptom, especially associated with weight loss and psychiatric problems, should have their use of L-dopa investigated. It is worth noting that in the case of our patient, the actual doses of L-dopa taken were nearly double those recorded in the medical notes.

Finally, patients with L-dopa addiction, both with and without IPD, represent a great challenge in management. The prognosis is recognised to be poor. In our patient’s case, Madopar was withdrawn only with her informed cooperation and that of her husband, who had given her drug treatment for many years. Other patients simply refuse to comply with drug changes and may even change specialists to secure an L-dopa supply. The successful outcome in this case is probably the exception rather than the rule.

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