Familial dystonia and visual failure with striatal CT lucencies

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SUMMARY A unique disorder is described in seven members of two families in whom dystonia was variably associated with subacute visual loss or asymptomatic optic atrophy, and striking bilateral symmetrical lucencies on CT scan, especially involving the putamen. It is possible that this is a variant of Leigh's disease. However, there were considerable differences between these patients and those with pathologically proven Leigh's disease. This condition must be excluded in all patients thought to have idiopathic dystonia, subacute visual failure similar to Leber's optic neuropathy, or a combination of these disorders.

In 1968 when Zeeman and Whitlock¹ reviewed the symptomatic dystonias, they stated that other neurological deficits are "invariably" present; that "dystonic features usually appear much later than the related nervous signs"; and that "for the experienced neurologist, the differentiation between dystonia musculorum deformans and symptomatic dystonias is... no problem". However with the advent of the CT scanning and modern biochemical techniques, several different types of secondary dystonia have been found to have an onset and early progression similar to idiopathic or primary torsion dystonia (dystonia musculorum deformans). A number of conditions, many of which feature dystonic movements and postures, have been described with bilateral lucent areas in the striatum on CT scan (table).

We report here a unique syndrome in seven patients from two families in which dystonia and symmetrical striatal lucencies on CT scan were variably associated with visual failure and other less prominent neurological signs. In the first family, a pure dystonic syndrome initially without other neurological abnormalities had suggested a diagnosis of idiopathic dystonia. Visual loss subsequently occurred and, in the

second family, it was the presenting feature in two patients. Of those progressive disorders which have been associated with a similar CT scan appearance, only Leigh's disease includes optic nerve involvement.^{16 17} Rondot and colleagues¹⁸ recently reported a single sporadic case of progressive dystonia with later onset of optic atrophy and bilateral striatal lucencies on CT scan. They concluded that their patient probably had Leigh's disease. However, in the absence of pathognomonic clinical laboratory features, the diagnosis of Leigh's disease can be confirmed only at necropsy. Without pathological confirmation it is not clear whether our patients represent an unusual variant of Leigh's disease or another, previously unrecognised disorder. A preliminary report of the first of these families has been presented in abstract form elsewhere.¹⁹

Family one (fig 1)

The parents of Family One were unrelated and there was no significant history of neurological disease in their relatives. The father was alive and well in his early 60s. The mother, at the age of 55 years, developed a rest tremor of the right arm. Examination (by AEL) revealed signs of typical idiopathic Parkinson's disease including a mask-like face, lack of arm swing, a rightsided rest tremor with mild akinesia and rigidity. She refused further investigation. The couple had four children. The first child was a stillborn female.

Case 1 (¹H₁)

The second child, a female, had an uncomplicated birth and normal development. At the age of 3.3 years she began to invert and dorsiflex the left foot on walking. Dystonia then slowly progressed to involve her left arm which would be

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Family 1

Fig 1 Pedigree of Family One. Symbols for this and the pedigree of Family Two (fig 5) are as follows:

- /○ = Unaffected male/female
- = Still birth
- ⊙ = Parkinsonism
- = Basal ganglia movement disorder (ie excluding cerebellar pyramidal etc)
- ⊙ = Movement disorder + optic atrophy
- ⊙ = Optic atrophy without movement disorder
- ⊙ = Deceased

held abducted and extended behind her with her fist clenched. Eighteen months after the onset of symptoms she had generalised dystonia which made speech unintelligible, interfered with swallowing, and left her chairbound. At the age of 5.5 years neurological examination revealed severe generalised dystonia with prolonged abnormal postures due to proximal dystonic spasms and distal "athetoid" movements. Other than coarse horizontal nystagmus on lateral gaze there were no additional neurological abnormalities and, within the limits of testing, she appeared very bright mentally. Normal laboratory findings included routine haematology, biochemistry, liver function tests, serum copper and caeruloplasmin. An EEG showed a focus of delta activity in the right temporal region with temporal spikes during sleep. Her physicians concluded that she most likely had a degenerative disease involving particularly the basal ganglia. In 1954 Sir Charles Symonds suggested a diagnosis of "torsion dystonia". The patient's motor disabilities slowly progressed without obvious mental deterioration until the

age of 8 years when she was admitted to hospital with a one week history of abdominal pain and vomiting. Examination showed a distended abdomen, fever, respiratory distress, prolonged opisthotonic posturing and generalised dystonia. Despite treatment with naso-gastric tube, fluid replacement, sedation and antibiotics she deteriorated over the next week and died of a presumed pneumonia. A necropsy was carried out in 1957; however, the results are no longer obtainable. One of us (AEL) contacted the patient's physician (Dr FJW Miller) who described the gross appearance of the brain as showing a striking symmetrical "honeycomb" appearance of the lentiform nuclei bilaterally.

Case 2 (¹II₂)

This 29-year-old female, the third child in Family One, had a normal birth and developmental history. She was well until the age of 8 years when she developed typical dystonic writer's cramp. Over the following 3 years the dystonia slowly progressed to involve face, trunk and all four limbs. Neurological examination showed no other abnormalities apart from generalised dystonia. Laboratory investigations, including serum and urine copper and serum caeruloplasmin, were normal. At the age of 9 years and again at 11, she had right Achilles tendon lengthening procedures. At age 11 years, despite the normal laboratory results, she was treated with penicillamine for several months without improvement. At age 14 years bilateral stereotactic thalamotomies resulted in minimal improvement of the dystonia, but left her with severe dysarthria. Between the age of 14 and 29 (when under the care of Dr JB Foster and Professor M Rawlins) there was little change in her symptoms. Mental function remained unaffected and she obtained a university degree in languages despite her motor disability. Various drugs did not improve her dystonia. However, the combination of baclofen 120 mg per day and diazepam 100 mg per day slightly lessened her abnormal foot posturing. Examination by us at age 29 years revealed severe generalised dystonia. Speech was unintelligible due to dystonia involving bulbar muscles; communication was carried out by a spelling board. She had some manual function and

Table Causes of bilateral basal ganglia* necrosis

Diagnosis	Distinguishing features
1. Leigh's disease ²	Motor disorders,† cognitive changes, brain stem signs, optic atrophy, vomiting, respiratory disturbances; acute, chronic, or relapsing.
2. Wilson's disease ³	Cognitive and psychological changes, motor disorders, Kayser-Fleischer rings, liver, kidney and corneal copper deposition; acute, chronic or relapsing.
3. Mitochondrial cytopathy ^{4, 5}	Retinopathy, external ophthalmoplegia, myopathy, ataxia, myoclonus, ragged-red fibres; chronic or relapsing.
4. Anoxia, prolonged hypotension, carbon monoxide or cyanide intoxication ^{4, 6, 7}	Preceding history, cognitive disturbance, motor disorders;† acute onset, occasionally delayed.
5. Familial holotrophic striatal necrosis ⁸	Mental retardation, motor disorders;† mainly chronic.
6. Acute neurological dysfunction following a febrile illness (Infantile striatal necrosis) ⁹	Seizures, bulbar motor disturbances, abnormal posturing, hypotonia, altered level of consciousness; acute onset.
7. Infections eg influenza ⁴	Systemic illness; subacute onset.
8. Haemolytic-uraemic syndrome ^{10, 11}	Systemic illness; subacute onset.
9. Vascular disease, sickle cell disease ³	Appropriate clinical setting, variable clinical features; acute onset.
10. Wasp sting encephalopathy ^{12, 13}	Coma, cognitive disturbances, motor disorders† acute onset.
11. Methanol intoxication ¹⁴	Exposure history, optic nerve and retinal changes, speech and swallowing disturbances; acute onset.
12. Acidosis eg methylmalonic aciduria ⁴	Systemic illness with acidosis; subacute onset or relapsing.
13. Head trauma ¹⁵	Injury; sometimes delayed motor effects; subacute or chronic onset.

*Includes striatum (caudate and putamen) and/or globus pallidus.

†Includes pyramidal, extrapyramidal and cerebellar disturbances.

she was able to bear weight but walked only with assistance. There was horizontal gaze-directed nystagmus most marked on looking to the right. The remainder of the neurological and general examinations were normal. Leucocyte enzyme studies and serum pyruvate and lactate without glucose challenge were normal. A CT scan (fig 2) showed some prominence of the Sylvian fissures and cortical sulci. In addition, there were symmetrical areas of low density in the basal ganglia in the region of the putamen. Similar smaller areas of low density were also seen adjacent to the body of the lateral ventricles anteriorly in the high parietal regions.

Case 3 ($^{1}II_3$)

This 23-year-old male, the fourth born of Family One, had a normal birth and development. He first complained of difficulty running at the age of 9 years. Over the next 3 years he developed generalised dystonia similar to that in his elder sister. By 16 years his speech was incomprehensible and he had become chairbound. At this time examination showed the picture of typical severe generalised dystonia with no other neurological abnormality. Between 16 and 23 years there was no obvious progression in motor disability. Like his sister he was highly intelligent and had obtained a university degree in classics. At the age of 23 years, over a period of 3 weeks, the patient noted a painless rapid bilateral deterioration in visual acuity. On examination visual acuity was 1/60 bilaterally with large central scotomas and normal peripheral fields. There was marked bilateral optic atrophy. Ocular pursuit movements were jerky; saccadic movements were slow with unsustained horizontal nystagmus on left

Fig 2 CT scan of Case 2 ($^{1}II_2$) showing symmetrical low density areas in putamen.

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gaze and vertical nystagmus on up-gaze. He had dystonia involving face, arms, trunk and legs (fig 3). Only single syllable words were comprehensible and he used a spelling board to communicate. He had some manual function remaining and was chairbound, unable to stand. There was generalised rigidity, but normal power and sensation and the deep tendon reflexes were brisk with flexor plantar responses.

Normal investigations included routine haematology and biochemistry, serum copper and caeruloplasmin, 24 hour urinary copper, serum lipid, serum protein electrophoresis, plasma aminoacid chromatography, urinary amino acids, mucopolysaccharides, sugar chromatography, cysteine, homocystine, phenylketonuria metabolites and porphyrins, leucocyte hexosaminidase A and B, beta galactosidase, arylsulphatase A, α -fucosidase and α -mannosidase, plasma glucuronidase and I-cell screen, serum phytanic acid, blood cytogenetics study, bone marrow aspiration, short Syn-athen stimulation test, EMG and nerve conduction studies, and slit lamp examination for Kayser-Fleischer rings. Electroretinogram and electro-oculogram showed no abnormality of the pigment epithelium or retinal photoreceptors. Visual evoked responses to flash stimuli showed low voltage delayed responses with an approximate latency of 220 ms to the first positive peak.

Fasting resting blood lactate was normal on repeated occasions, but blood pyruvate was elevated one and one half to four times the upper limit of normal on four separate occasions and was normal on a fifth. During a standard glucose tolerance test blood pyruvate rose to 222 μ mol/l (normal less than 135) one hour after the glucose load and lactate levels remained normal. An intravenous alanine load of 25 mg/kg (1.15 g) produced a normal response in glucose, pyruvate and lactate levels. Platelet pyruvate dehydrogenase levels (Dr A Chapman) were within normal limits (0.15 nmol/min/mg protein; normal range 0.05–0.20 nmol/min/mg protein). Muscle biopsy (Dr JA Morgan-Hughes) showed normal histology, with the exception of a slight excess of lipid droplets. Reactions for phosphorylase, myo-adenylate deaminase and cytochrome oxidase were normal. Oxygen electrode studies were normal

Fig 3 Photograph of Case 3 ($^{1}II_3$) mild dystonia of bulbar muscles seen in picture worsens markedly when attempting to speak. Dystonia in arms is evident. He is wheelchair bound because of severe dystonia in the legs.

as were mitochondrial cytochromes. Intra-mitochondrial enzyme studies showed a high basal activity of the pyruvate dehydrogenase complex (62 nmol/min/mg mitochondrial protein) with a further rise to 89 nmol/min/mg after activation. Mitochondrial NAD levels and activities of NADH ferricyanide reductase and citrate synthetase were also normal. A CT scan (fig 4) showed areas of low attenuation in the putamina and the heads of the caudate nuclei with slight enlargement of the lateral ventricles. The optic nerves were normal.

On the basis of the CT scan abnormalities, bilateral optic atrophy, the elevated blood pyruvate and the family history

a diagnosis of Leigh's disease was suggested. The patient was seen in consultation by Dr Denis Leigh who agreed that this was the most likely possibility. He was treated with thiamine, tetrahydrofurfuryl disulphide (TTFD) 300 mg and riboflavin 30 mg per day. Three months later neurological examination revealed no change from his previous state.

Family two (fig 5)

This family contains four cases of the disease in a single generation.

Case 4 ($^2IV_{11}$)

This 21-year-old male was referred because of severe visual failure. He was first seen in May 1982. His parents were and are healthy; he had five normal siblings. His mother was well during pregnancy and the delivery was normal. Walking and talking were said to be delayed but he read at a normal age. He had had difficulty with fine finger movements as long as the family could remember. At the age of 8 years it was noted that walking was becoming difficult and that he fell more frequently than normal. The motor symptoms had been slowly progressive ever since. Friends had commented recently that his speech seemed to be slurred and he had noticed some difficulty in swallowing solids. Eleven months before presentation, at the age of 20 years, he developed in the course of 3 days, severe visual loss in the right eye, and in the following week, similar affection of the left eye. There had been no recovery.

On examination the visual acuities were VR counting fingers at 1m, VL 1/60. There were large bilateral central scotomata. Both optic discs were very pale and there was extensive retinal nerve fibre loss. There was a first degree horizontal jerk nystagmus on gaze to right and left. The glabella tap sign was present. Movements of the tongue were slow. There was cogwheel rigidity in the arms, right more than left, and paratonia in the legs. There was impairment of fine finger movements, right more than left. Power and co-ordination were however normal. The tendon jerks were brisk and symmetrical, and the plantar reflexes weakly extensor. There was no sensory abnormality and the peripheral nerves were not enlarged.

Investigations included VEPs (Dr Eva Perringer) which were very small and not reproducible; fixation was poor. The SEP in response to median nerve stimulation showed normal peripheral and cortical components and there was no definite abnormality in the AEP. Nerve conduction studies (Dr RS Kocen) were normal in arm and leg. Psychometry (Dr Abdallat) revealed a verbal IQ of 111 (WAIS) and no evidence of localised or generalised intellectual deterioration. An amino acid screen of the urine revealed no abnormality; reducing substances were absent. Liver function tests were normal, although the alkaline phosphate (185 IU/l) was just above the upper limit of normal (170 IU/l). There were normal serum levels of caeruloplasmin and copper. A CT scan carried out at the King Hussein Medical Centre in July 1981 had revealed symmetrical lucencies in the basal ganglia (fig 6).

He was re-examined in May 1984 (WIMcD). There had been no symptomatic change since 1982. The visual acuities were reduced to counting fingers bilaterally. There were large bilateral central scotomas. Both optic discs were very

Fig 4 CT scan of Case 3 (1II_3) showing symmetrical low attenuation areas in putamen and heads of caudate nuclei.

Family 2

Fig 5 Pedigree of Family Two. See legend of fig 1 for symbols.

pale. The vessels on the discs were arranged in an anomalous fashion and nearby on the retina they were unusually tortuous. There were bilateral afferent pupillary defects. There was a mild slurring dysarthria. There was mild cogwheel rigidity in the arms but not the legs. There was moderate proximal and distal weakness in the arms. The tendon reflexes were present and symmetrical and the plantar reflexes extensor. There was a dystonic posture of the outstretched arms (hyperextension of the fingers and thumbs). Fine finger movements and writing were slow. As he walked, the trunk appeared to rotate on the pelvis and there was dystonic posturing of the left arm during heel/toe walking.

Case 5 (2IV_4)

This 13-year-old boy was referred in June 1980 because of a progressive motor disturbance since childhood. He was a second cousin of Case 4. His parents were healthy and he had four healthy siblings aged 20, 19, 17 and 6 years. His mother had been well in pregnancy and the delivery was normal. At the age of 2 months his mother noticed that the right foot was turned inwards. He walked at 15 months. At the age of 2 years a squint was noticed and he was prescribed spectacles; it was said at that time that he had optic atrophy. His walking gradually deteriorated from early childhood, especially after the age of 6 years. When he was about 7 years he had a tendon transplant in the right leg. At the time of presentation he noticed that the movements of the left hand were particularly slow and that his writing and speech were slow. He had always been unable to run. He was, however, doing well at school.

Fig 6 CT scan of Case 4 ($^2IV_{11}$) showing symmetrical lucencies in the putamen bilaterally.

On examination the visual acuity was correctable to VR 6/9, VL 6/6 (Mr David Taylor). Colour vision was normal and the fields were full to a 1 mm target at 1 m. Both optic discs were pale. Apart from a latent divergent squint, the eye movements were normal. Speech was slow and slurred. He had a dystonic gait and all movements were slow, particularly in the left hand. The right leg was smaller than the left. There was a mild increase in tone, more marked in the legs than the arms. There was moderate bilateral weakness, right greater than left. The finger nose and heel shin tests were slowly performed but there was no ataxia. The tendon reflexes were sluggish but symmetrical. The plantar reflexes were extensor. Sensation was intact. There was a scoliosis and the neck was short. Investigations included a VEP (Dr WM Carroll) which was abnormal, indicating impairment of function in the central and temporal paracentral fields; the latencies were normal (right eye 114 ms, left eye 107 ms). Nerve conduction studies (Dr NMF Murray) were normal in the legs. A random blood glucose was normal. The serum alkaline phosphatase was 366 IU/l (upper limit of normal, 170 IU/l). Serum proteins (including electrophoresis), bilirubin and the alanine amino transferase were normal. An amino acid screen of the urine revealed no abnormality, and reducing substances were absent. The cerebrospinal fluid contained no white cells, a sugar of 3.1 mmol/l, and a protein of 260 mg/l of which the IgG represented 5.4%.

Plain radiographs revealed a large cranial vault and a wide cervical canal. A myelogram was however normal. A CT scan at the King Hussein Medical Centre in June 1979 had revealed symmetrical lucencies in the basal ganglia (fig 7).

He was re-assessed in May 1984 (WIMcD). He now walked with difficulty. Speech was slurred and fine movement and writing much slower. He was doing well at school and had just taken A levels. On examination the visual acuities were 6/12 bilaterally with glasses. Both optic discs were pale. The vessels on the disc were arranged in an anomalous fashion and nearby on the retina they were unusually tortuous. The pupils were normal. There was moderate plastic rigidity in the arms with a cogwheel component on the left. The outstretched fingers and thumbs were hyperextended. There was some shortening of the right leg but the tone in both legs was normal on the couch. He walked on his toes with marked flexion of the knees and adduction of the thighs. The tendon jerks were depressed in the arms and brisk in the legs and the plantar reflexes were extensor.

Case 6 (2II_7)

This 22-year-old female university student was referred to Dr Roman Kocen in January 1973 because of difficulty in walking. Her parents were healthy. She is the sister of Case 7, a first cousin of Case 5 and a second cousin of Case 4. She has another sister and a brother who are well. Her development was normal until about the age of 11 or 12 when she gradually developed difficulty with walking and slurring of speech which have persisted.

On examination the skull was rather small. The visual fields and fundi were normal. The eye movements and pupils were normal. There was slight bilateral facial weakness. Tongue movements were slow. There was a slight increase in tone in the forearms, left more than right. There was no weakness. There was impairment of fine movements, but no definite ataxia. The right leg was smaller than the left. The

tendon reflexes were symmetrical and the plantar reflexes flexor. Sensation was normal. Investigations included an electroencephalogram which was normal. Nerve conduction studies revealed no abnormality in the leg. Liver function tests were reported normal, and the serum copper and caeroplasmin levels were also normal. Skull radiographs revealed no abnormalities.

She was re-assessed in May 1984 (WIMcD). There had been little or no symptomatic change since 1973. On examination the visual acuities were VR 6/6; VL 6/12 with glasses. The optic discs were not pale but the vessels were arranged anomalously and were unusually tortuous on the nearby retina. Pursuit movements of the eyes were broken up. There was a slurring dysarthria so severe that speech was difficult to understand. The tongue movements were slow. There was hyperextension of the outstretched fingers and thumbs. There was cogwheel rigidity in all four limbs, slight in the arms and marked in the legs. Tendon reflexes were brisk and the plantar reflexes extensor. Walking was slow with marked adduction of the thighs and a tendency to rotate the pelvis; the arms did not swing.

Case 7 (2IV_9)

This 15-year-old boy is brother of Case 6, first cousin of Case 5, and second cousin of Case 4. He was referred to Mr Michael Sanders in August 1973 because of visual loss. Six months earlier he had been examined by an ophthalmologist and glasses had been prescribed and no other abnormality was commented on. In the summer of 1973 he developed severe visual loss over the course of one month.

On examination the visual acuities were VR counting

Fig 7 CT scan of Case 5 (2IV_4) showing symmetrical lucencies in the putamen bilaterally.

fingers and VL 2/60. He was unable to read any colour charts with the right eye and only the first with the left eye. The visual fields revealed large bilateral central scotomata. The right optic disc was grossly atrophic and the left optic disc showed a marked temporal pallor. There were bilateral afferent pupillary defects but the eye movements were normal. He was seen in consultation by Dr Roman Kocen who found a left extensor plantar response but commented that the appearance of the feet was different on the two sides. There were no other neurological abnormalities.

Investigations included a blood count which was normal. The CSF contained 180 mg/l of protein, 1 white cell/mm³, a negative Pandy and no change in the Lange. Serology for syphilis was negative. Plain radiographs of the skull, tomograms of the optic canals and a left carotid arteriogram were normal. A lumbar air encephalogram revealed considerable dilation of the left lateral ventricle and slight dilation of the right lateral ventricle. The transverse diameter of the third ventricle was also increased. The aqueduct and the fourth ventricle, the basal cisterns and the cortical sulci were normal.

He was reassessed in May 1984 (WIMcD) and was symptomatically unchanged. On examination the visual acuities were VR 1/60, VL 1/60 uncorrected. There were large bilateral central scotomas. There was a severe bilateral optic atrophy. On the disk the vessels were arranged in an anomalous way and on the nearby retina they were unusually tortuous. There was no dysarthria. Tone, power and co-ordination were normal in the limbs. There was slight but definite weakness of hip flexion bilaterally. The tendon reflexes were present and symmetrical and both plantar reflexes were extensor. Gait was normal.

Discussion

This unique disorder combines prominent dystonic movements and postures, subacute visual failure, normal intelligence, minimal additional neurological abnormalities such as pyramidal tract signs, and the striking CT scan appearance of bilateral symmetrical striatal lucencies. Each of the two major clinical features, dystonia and visual loss, occurred separately or in combination in different members of the two families.

The possible differential diagnosis of the cause of this condition is considerable. In Family One, Case 3's clinical examination, family history and high intellectual capacity were typical of the autosomal recessive idiopathic (primary) dystonia commonly seen in Ashkenasi Jews, until optic atrophy developed. The primary pallidal degenerations²⁰ also may present with dystonia indistinguishable from that seen in idiopathic torsion dystonia. However, optic atrophy and the lytic lesions in basal ganglia on CT scan excluded both these diagnostic possibilities. Another condition somewhat similar to that seen in Family One was described in five members of two families by Miyoshi and colleagues⁸ as "Familial Holotopistic Striatal Necrosis". Here bilateral symmetrical necrosis of cau-

date and putamen (which would have given CT scans similar to those demonstrated in our cases) was associated with a clinical syndrome comprised of mental retardation, severe dystonia and athetosis, spasticity, dysphagia and dysarthria. The progressive movement disorder seen in their cases was reminiscent of that occurring in Family One. However, unlike our patients, mental retardation was prominent, all had normal extra-ocular movements with no nystagmus, and none had involvement of the optic nerves or tracts. Visual disturbances occurring in a patient with dystonia immediately raises the possibility of Hallervorden-Spatz disease. Here the visual failure may be due to either retinitis pigmentosa or optic atrophy.²¹ In contrast to the preserved intellect in our patients, cases of Hallervorden-Spatz disease usually develop profound dementia. CT scans in this condition have demonstrated widespread atrophic changes²² without the symmetrical lucencies seen in our patients. Recently, Swaiman and his colleagues²³ described two unusual patients with sea-blue histiocytes and lymphocytic cytosomes, diagnosed as having Hallervorden-Spatz disease on the basis of radionucleotide iron scanning, who had bilateral basal ganglia lucencies on CT scan. However, the location and nature of these lesions was most atypical for Hallervorden-Spatz disease, in which the globus pallidus is particularly affected and the striatum usually is spared.

CT scan abnormalities similar to those seen in our patients have been described in a number of other conditions. In addition to the disorders reviewed in the table, such changes have been reported briefly in rare, poorly documented cases of Parkinsonism and striatonigral atrophy,²⁴ and in the unusual cases of Swaiman *et al*²³ thought to have Hallervorden-Spatz disease. Patients with Wilson's disease may have prominent dystonia and similar CT scan basal ganglia lucencies.³ However, the presence of optic atrophy and the absence of Kayser-Fleischer rings and abnormalities of copper and caeruloplasmin on repeated determinations made this diagnosis untenable in our cases. Detailed laboratory assessment excluded other "neurometabolic" disease in which prominent childhood onset dystonia rarely may occur. These include the juvenile metachromatic leukodystrophy,²⁵ chronic hexosaminidase A and B deficiency,²⁶ chronic GM₁ gangliosidosis,²⁷ GM₂ gangliosidosis,²⁸ a mucopolysaccharidosis with keratin-sulfuria described by Maroteaux,²⁹ ceroid lipofuscinosis (personal observation), neurovisceral storage disease with vertical supranuclear ophthalmoplegia,³⁰ the Lesch-Nyhan syndrome,³¹ glutaric aciduria type I,³¹ and homocysteinuria.³² The pathological changes which occur in these disorders are not known to give rise to the large symmetrical CT

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scan lucencies seen in our patients.

Of those disorders listed in the table the combination of this CT scan appearance with a movement disorder and optic atrophy strongly suggests a diagnosis of Leigh's disease.³³ Due to the frequent involvement of the basal ganglia, particularly caudate and putamen, a wide range of movement disorders may occur in Leigh's disease. These include a Parkinsonian akinetic-rigid syndrome, and a variety of dyskinesias such as chorea, ballism, dystonia or athetosis, myoclonus and tremor. Dystonia has been mentioned at some time in the course of the illness in at least 20 patients described in the literature, out of 34 reported to have movement disorders.^{2 16-18 34-48} However, unlike our cases, in most patients reported, movement disorders usually did not dominate the clinical picture and rarely have they been the presenting feature of the disease. Indeed only three began with dystonia.^{18 48} However, it must be emphasised that no pathological confirmation of the presumptive clinical diagnosis of Leigh's disease was available for any of these cases.

Although optic atrophy is mentioned in four of these patients with dystonia,^{2 18 36 37} none presented with visual failure as was seen in our Case 4. In our patients, the time course, severity and persistence of the visual loss was reminiscent of Leber's optic neuropathy. All of the patients were not seen in the acute phase of their illness, so we cannot say whether the "vasculitic" retinal changes characteristic of the early stages of Leber's disease⁴⁹ (which differ from the tortuosity of the vessels seen in Family Two) were present. The presence of asymptomatic optic atrophy in at least one member of Family Two suggests, as in Leigh's disease,^{50 51} that visual involvement is part of the overall clinical picture.

Our cases have both similarities but also considerable differences from the pathologically proven cases of Leigh's disease reported to date. In view of its broad clinical spectrum, Leigh's disease may not be a single entity and it may be more correct to speak of Leigh's syndrome which could include the patients reported here. The aetiology of Leigh's disease is unknown, although most studies have suggested an impairment of pyruvate metabolism.^{40 45 52-55} Review of the clinical descriptions of many cases said to have Leigh's disease reveals a possible overlap with the "mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes" (MELAS) syndrome reported recently.⁵⁶ Leber's optic neuropathy also has been linked recently to a disturbance of mitochondrial function.⁵⁷

Since the preparation of this paper, Novotny and his colleagues⁵⁸ have reported a single large pedigree similar to those reported here. Seven members had hereditary optic neuropathy and 14 had a "neuro-

degenerative" disorder dominated by dystonia. CT scan showed striatal "degeneration" with putaminal lucencies. Unlike our patients, intellectual impairment, short stature and myopathic features were also present. The mode of inheritance was compatible with maternal transmission or cytoplasmic inheritance. Study of restriction endonuclease DNA polymorphism patterns of mitochondrial DNA in affected individuals supported the conclusion that this disease was a mitochondrial pathology. With the exception of Case 4 in Family Two, the inheritance pattern in both our families also suggests maternal transmission as occurs for mitochondrial DNA, although the pedigrees are too small to exclude completely all other possible modes of inheritance (see ref 59 for discussion). The elevation of blood pyruvate in our Case 3 and the subsequent visual failure similar to Leber's optic neuropathy also raise the question whether the disorder reported in our patients may have an underlying disturbance of mitochondrial function. However, muscle biopsy studies in Case 3 failed to reveal any abnormalities in the enzyme systems analysed. Future study of mitochondrial structure and function, as well as genetic analysis, may provide an insight into the questions of mode of inheritance and aetiology.

One important reason for reporting these cases is to highlight the longstanding pure dystonic syndrome in Family One which mimicked idiopathic dystonia for many years until Case 3 developed subacute visual failure. Without CT scan, laboratory investigation and long-term follow-up, the diagnosis of idiopathic dystonia is at best unreliable. This fact is crucial in the interpretation of epidemiological studies in familial dystonia. Some of the cases cited in Eldridge's excellent review of the torsion dystonias,⁶⁰ particularly those with "atypical" dystonia, may have had the disorder reported here, as may other cases of "dystonia musculorum deformans" with unusual associated neurological features, for example the patient described by Rosenberg *et al* with ophthalmoplegia and dystonia.⁶¹ Our experience with these cases, and with several other examples of symptomatic dystonia which for a time were clinically indistinguishable from idiopathic dystonia, encourages us to investigate thoroughly all cases of dystonia for a possible neurometabolic cause including, now, this unusual disorder with visual failure and striatal lucencies on CT scan.

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