A 26-year-old woman presented after developing slurred speech and drooling overnight. She had a 6-month history of tiredness and poor concentration, and episodes of loss of consciousness accompanied by paraesthesia of her hands, feet and mouth. Occasionally, one arm would ‘hang in a strange way’.

Her mother reported a preceding personality change with angry outbursts and anxiety, although these had largely subsided after starting antidepressants. Her only past history was a severe depressive episode in her teens and a difficult and occasionally abusive family life. There was no family history of neurological disease.

On examination, she was alert and orientated. There was mild dysarthria but normal motor, sensory and coordination examination.

**Question 1**

What is the likely differential diagnosis?

**Comment**

The pattern of neurological features does not immediately suggest any single lesion and, with no objective examination findings, might easily be construed as functional or psychosomatic. The initial clinical suspicion was of a psychiatric presentation, given her personal history; however, her mood had recently been more stable and there was no obvious psychosocial precipitant for this acute presentation.

The possibilities of reflex (vasovagal) syncope or hyperventilation syndrome were suggested to account for the loss of consciousness with facial paraesthesia. Vasovagal syncope seemed unlikely with no presyncopeal symptoms or triggers, such as prolonged standing, dehydration or stress. Hyperventilation syndrome was also unlikely, as forced hyperventilation did not reproduce the symptoms.

On presentation, the patient herself thought she was having a stroke. Despite the acute onset and nature of her symptoms, her age, examination findings and lack of risk factors made this unlikely. Stroke mimics can occur in young people and form part of the differential diagnoses. These include space-occupying lesions, migraines, focal seizures, multiple sclerosis and periodic paralysis.

**Question 2**

What would you do next?

**Comment**

Routine blood tests showed only mild thrombocytopenia. There was no postural hypotension. She continued taking antidepressants and underwent cognitive behavioural therapy, which helped in stabilising her mood.

After she developed widespread arthralgia and dystonic tremor of the left hand, as well as persistent fatigue, slurred speech and episodes of loss of consciousness, her medical team requested a specialist neurological opinion.

The neurologist noted the above findings in addition to horizontal diplopia, worse in primary position, and arranged repeat bloods with 12-lead ECG, EEG and MR scan of brain (table 1).

**PROGRESSION**

Over the next 18 months, she reported more prominent diplopia with occasional blurred vision, as well as frequent dystonic posturing, particularly of the left hand. She suffered extreme fatigue with variable confusion and irritability, exacerbated by chronic headaches. In addition, she developed widespread arthralgia. There was a marked decline in her handwriting, which became progressively smaller and more illegible.

On examination, she had a markedly ataxic gait and worsening coordination.
Upper limb examination showed cogwheeling reinforced by synkinesis, and mild dysdiadochokinesia. Reflexes and muscle bulk remained largely intact. A speech and language therapist felt that her fluctuating slurred speech with mild word-finding problems was a ‘Parkinsonian-like dysarthria’; there was also dysfunctional coordination of swallowing. The patient reported her speech and swallowing worsened with tiredness or anxiety. Her depression deepened, with frequent mood swings and agitation.

Comment
The widespread symptoms and their protracted onset might suggest a genetic, inflammatory or degenerative condition. We explored several differential diagnoses.

- **Multiple sclerosis.** Her age, sex and dissemination of neurological symptoms in space and time indicate the need to consider multiple sclerosis in the differential diagnosis; however, psychiatric symptoms are unusual as presenting features and arthralgia is not a feature.

- **Wilson’s disease.** The combination of neurological symptoms with arthralgia might suggest Wilson’s disease, although the onset is relatively late and the fluctuating dystonic posturing would be atypical. In addition, there was no relevant family history and copper studies and liver function tests were both reported as normal.

- **Juvenile Parkinson’s disease.** This was highlighted given the Parkinsonian-like dysarthria and the later development of micrographia and cogwheeling with synkinesis. However, there was no resting tremor or other physical features of Parkinsonism.

- **Mitochondrial disorder, for example, MELAS, adult-onset Leigh’s syndrome.** These are characterised by maternal inheritance, poor growth, myopathy and learning difficulties. An example we considered was MELAS, an umbrella disorder comprising mitochondrial myopathy, encephalomyopathy, lactic acidosis and stroke-like symptoms. Leigh’s syndrome, a subacute sclerosing encephalopathy, usually presents in infancy but clinical manifestations depend on the site of neuropathological involvement. It may manifest initially in adults as a movement disorder, including multifocal dystonia and pyramidal weakness, irritability, fatiguability and cognitive decline.

- **Variant Creutzfeldt–Jakob disease (vCJD).** This presentation would be atypical for vCJD, which produces myoclonic jerks and rapidly-progressive dementia over 12–14 months. Nevertheless, dysphasia, anxiety, depression, seizures and ataxia are prominent features, with psychiatric symptoms often preceding neurological ones.

- **Postencephalitic Parkinsonism (Von Economo’s disease).** This is a rare diagnosis; outbreaks followed influenza pandemics, the last being in the early 20th century. In these cases, viral encephalitis probably triggers degeneration of the substantia nigra, causing Parkinsonism. There are occasional sporadic cases.

- **Myeloma.** Although classically affecting older people, up to 2% of cases occur between 20 and 40 years. The symptoms vary but those suggesting myeloma in this case include fatigue and weakness (hypercalcaemia), headache and visual changes (hyperviscosity), and parasthesia (amyloid infiltration of peripheral nerves).

- **Autoimmune encephalitides.** Several recently described autoimmune and paraneoplastic disorders, particularly anti-NMDA receptor encephalitis, have features in common with our patient. This presents with neuropsychiatric symptoms, dyskinesia, seizures and dysautonomia. Anti-AMPA receptor encephalitis typically presents with limbic encephalitis or with isolated psychiatric symptoms. Antiglycine disease can cause ataxia, often with prominent stiffness and other features, and mGluR1 disease may also show ataxia. These conditions are important to consider early as outcome is better with early treatment and many are associated with underlying neoplasms.

Five years after her initial presentation, there was still no definitive diagnosis. We performed some further investigations (table 2).

Three years after her initial presentation, during which time her vision had continued to deteriorate, an optician documented ‘yellow-brown deposits circumferentially in the inner layer of the peripheral cornea’.

**Question 3**
How might these developments affect the differential diagnoses and what further investigations may help?

**Question 4**
What is the diagnosis and how would you confirm it?

**Comment**
The diagnosis is Wilson’s disease. The corneal deposits represent Kayser–Fleischer rings which, although no longer considered pathognomonic of Wilson’s

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**Table 1  Investigation results**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full blood count</td>
<td>Normal, except thrombocytopenia</td>
</tr>
<tr>
<td>Liver function tests</td>
<td>Normal</td>
</tr>
<tr>
<td>Urea and electrolytes</td>
<td>Normal</td>
</tr>
<tr>
<td>Copper studies</td>
<td>Normal serum copper and caeruloplasmin</td>
</tr>
<tr>
<td></td>
<td>Non-caeruloplasmin-associated copper 17 μg/dL (raised; target &lt;10)</td>
</tr>
<tr>
<td>Serum creatine kinase</td>
<td>Normal</td>
</tr>
<tr>
<td>Amino acid analysis</td>
<td>Slightly raised tyrosine, indicative of possible liver involvement</td>
</tr>
<tr>
<td>12-Lead ECG</td>
<td>Normal</td>
</tr>
<tr>
<td>EEG</td>
<td>Normal</td>
</tr>
<tr>
<td>MR scan of brain</td>
<td>Altered signal in basal ganglia, pons and dorsal midbrain</td>
</tr>
</tbody>
</table>

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This was highlighted given maternal inheritance, poor growth, myopathy and learning difficulties. An example we considered was MELAS, an umbrella disorder comprising mitochondrial myopathy, encephalomyopathy, lactic acidosis and stroke-like symptoms. Leigh’s syndrome, a subacute sclerosing encephalopathy, usually presents in infancy but clinical manifestations depend on the site of neuropathological involvement. It may manifest initially in adults as a movement disorder, including multifocal dystonia and pyramidal weakness, irritability, fatiguability and cognitive decline.

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**Question 3**
How might these developments affect the differential diagnoses and what further investigations may help?

**Question 4**
What is the diagnosis and how would you confirm it?

**Comment**
The diagnosis is Wilson’s disease. The corneal deposits represent Kayser–Fleischer rings which, although no longer considered pathognomonic of Wilson’s
logical signs of Wilson disease, classically occur in affected patients. They are especially prevalent (up to 95%) in those with neurological manifestations. She was referred to a specialist centre where repeat caeruloplasmin, serum and urinary copper, and a D-penicillamine challenge test confirmed the diagnosis. Subsequent DNA analysis showed a homozygous H1069Q mutation in the \textit{ATB7} gene.

Despite her relatively late and atypical presentation, clinicians should consider rigorous exclusion of Wilson’s disease in all young people with the combination of a movement disorder, psychiatric disturbance and arthralgia, because the condition is so treatable. Early treatment is essential before there is irreversible brain damage through copper deposition.

In their seminal series of 136 patients with neurological signs of Wilson’s disease, Walshe and Yealland\textsuperscript{4} found that the age at onset of neurological features was 9–40 years (median 16). Overall, 23% of patients had already an episode of liver damage as early as 3 years of age. In a further 114 cases, the diagnosis was already made before the onset of neurological symptoms. They divided the neurological group into four predominant clinical pictures according to the nature of the movement disorder: 45% were Parkinsonian, 24% ‘pseudosclerotic’, 15% dystonic and 11% choreic. Dysarthria, tremor, personality change and drooling were common initial symptoms. All patients with neurological disorders had corneal pigmentation, although not necessarily complete rings.

In our case, other pointers to the diagnosis included the initial serum copper level, which, although deemed normal at the time, was at the lower limit of normal. The serum caeruloplasmin level was within limits but had been measured using an immunological assay, as performed by many UK laboratories. Importantly, there is growing evidence to suggest that immunological assays overestimate caeruloplasmin levels, and that enzymatic assays may be preferable.\textsuperscript{3}

There was also thrombocytopenia in the initial bloods. Although non-specific, there has long been a recognised minor association between Wilson’s disease and thrombocytopenia.\textsuperscript{4} This patient may be considered as having a late presentation, being diagnosed at age 31 years, although the literature generally regards onset of Wilson’s disease after the age of 40 years as being of ‘late onset’.

MR brain scan findings in Wilson’s disease are widespread and variable, involving most structures in varying combinations but most commonly involving the basal ganglia, midbrain, pons and cerebellum. Most typically, there is symmetrically increased signal in the putamen, globus pallidus, thalamus, caudate head, dorsal midbrain and pons. There can also be more widespread involvement, including of the cortical white matter with diffuse brain atrophy and ventricular enlargement, but rarely the medulla.\textsuperscript{5} Signal change together in the basal ganglia, thalamus and brainstem strongly suggests Wilson’s disease. The so-called ‘face of the giant panda and her cub’ and ‘double panda’ signs are rare, but very typical of Wilson’s disease.\textsuperscript{6}

Skeletal changes on plain X-ray are common but not diagnostic. They include evidence of osteomalacia, osteochondritis, osteoarthritis and bone fragmentation, particularly of the lumbar and cervical spine, hands, wrists, elbows, knees and feet.

The difficulty in diagnosing this case arose from the atypical presentation and from lack of clarity regarding the exclusion of Wilson’s disease. Copper studies are commonly used in clinical practice to deem a diagnosis of Wilson’s disease unlikely, as done here (table 3).\textsuperscript{7} Unfortunately, this practice may lead to a missed diagnosis. Although rapidly and cheaply obtained in most hospitals, the sensitivity of these

\begin{table}
\centering
\caption{Further investigations}
\begin{tabular}{|l|l|}
\hline
\textbf{Investigation} & \textbf{Result} \\
\hline
\textit{B}_{12} \text{ and folate} & Normal \\
Leucocyte and plasma enzymes & \\
Serum antinuclear antibody & \\
Serum protein electrophoresis & \\
Urine porphyrin screen & \\
Urine organic acids & \\
Cerebrospinal fluid & \\
Evoked potentials & \\
Repeat MR scan of brain & \\
Muscle biopsy & \\
Amino acid levels & \\
\hline
\end{tabular}
\end{table}
tests for Wilson’s disease may be inadequate. A recent study identified the sensitivities for detecting Wilson’s disease were 85% for serum copper and 83% for serum caeruloplasmin. Thus, using these tests alone leaves a significant proportion of people with undetected disease.

Table 3 Routine tests for diagnosing Wilson’s disease

<table>
<thead>
<tr>
<th>Test</th>
<th>Typical finding</th>
<th>False ‘negative’</th>
<th>False ‘positive’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum caeruloplasmin</td>
<td>Decreased by 50% of lower normal value</td>
<td>Normal levels in patients with marked hepatic inflammation</td>
<td>Low levels in:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overestimation by immunological assay, pregnancy and oestrogen therapy</td>
<td>▶ malabsorption</td>
</tr>
<tr>
<td>24-h urinary copper</td>
<td>&gt;1.6 μmol/24 h in adults&gt;0.64 μmol/24 h in children</td>
<td>Normal levels if:</td>
<td>▶ aceruloplasminaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ incorrect collection</td>
<td>▶ heterozygotes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▶ children without liver disease</td>
<td>▶ hepatocellular necrosis</td>
</tr>
<tr>
<td>Serum ‘free’ copper</td>
<td>&gt;1.6 μmol/L</td>
<td>Normal if caeruloplasmin overestimated by immunological assay</td>
<td>▶ cholestasis</td>
</tr>
<tr>
<td>Hepatic copper</td>
<td>&gt;4 μmol/g dry weight</td>
<td>Due to regional variation in:</td>
<td>▶ contamination</td>
</tr>
<tr>
<td>Kayser–Fleischer rings by slit-lamp exam</td>
<td>Present</td>
<td>Absent</td>
<td>Primary biliary cirrhosis</td>
</tr>
</tbody>
</table>

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Various tests may support a diagnosis of Wilson’s disease, including 24-h urinary copper (53% sensitivity in the above study), D-penicillamine challenge, DNA analysis and hepatic parenchymal copper content by liver biopsy. There are over 300 reported mutations in the ATP7B gene; most patients are compound heterozygotes. Gene sequencing is commonly used in populations with well-defined mutations, to test family members where the mutation is already known or in cases where conventional tests have not led to a clear diagnosis. A recent study of 181 clinically and biochemically confirmed cases of Wilson’s disease from the UK identified mutations in the ATP7B gene in 98%. The commonest mutation was H1069Q (seen in our patient) in 19%, a mutation known to be common in those of European descent.

Recent practice has moved away from reliance on individual investigations and towards scoring systems based on clinical and laboratory findings. Table 4 outlines one widely used example of these, developed at the 8th international meeting on Wilson’s disease.

### Question 5

**How would you manage this patient?**

**Comment**

Several drugs are commonly used to treat Wilson’s disease. These are maintained lifelong once the diagnosis is established, although there are few high-quality trials supporting these medications.

D-penicillamine and its newer alternative trientine each acts by chelating copper and increasing urinary copper excretion. Patients should receive 25–50 mg of supplemental pyridoxine along with D-penicillamine.

### Table 4  Scoring system for diagnosis of Wilson’s disease

<table>
<thead>
<tr>
<th>Typical clinical symptoms and signs</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kayser–Fleischer rings</td>
<td>Liver copper (in the absence of cholestasis)</td>
</tr>
<tr>
<td>Present</td>
<td>&gt;5×upper limit of normal (&gt;4 μmol/g)</td>
</tr>
<tr>
<td>Absent</td>
<td>0.8–4.0 μmol/g</td>
</tr>
<tr>
<td></td>
<td>Normal (&gt;0.8 μmol/g)</td>
</tr>
<tr>
<td></td>
<td>Rhodanine-positive granules*</td>
</tr>
<tr>
<td>Neurological symptoms†</td>
<td>Urinary copper (in the absence of acute hepatitis)</td>
</tr>
<tr>
<td>Severe</td>
<td>Normal</td>
</tr>
<tr>
<td>Mild</td>
<td>1–2×upper limit of normal</td>
</tr>
<tr>
<td>Absent</td>
<td>&gt;2×upper limit of normal</td>
</tr>
<tr>
<td>Serum caeruloplasmin</td>
<td>Normal but &gt;5×upper limit of normal after D-penicillamine</td>
</tr>
<tr>
<td>Normal (&gt;0.2 g/L)</td>
<td>Mutation analysis</td>
</tr>
<tr>
<td>0.1–0.2 g/L</td>
<td>On both chromosomes detected</td>
</tr>
<tr>
<td>&lt;0.1 g/L</td>
<td>On one chromosome detected</td>
</tr>
<tr>
<td>Coombs’-negative haemolytic anaemia</td>
<td>No mutations detected</td>
</tr>
<tr>
<td>Present</td>
<td>Evaluation:</td>
</tr>
<tr>
<td>Absent</td>
<td>Diagnosis established</td>
</tr>
<tr>
<td>Total score</td>
<td>Diagnosis possible, more tests needed</td>
</tr>
<tr>
<td>4 or more</td>
<td>Diagnosis very unlikely</td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>2 or fewer</td>
<td></td>
</tr>
</tbody>
</table>

*If no quantified liver copper available.
†Typical abnormalities at MR scan of brain.
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Practice points

- Neuropsychiatric presentations with arthralgia or movement disorder should suggest the possibility of Wilson’s disease.
- Clinicians should have a low threshold for testing for Wilson’s disease due to its potential treatability and better outcomes with early treatment.
- Serum copper and caeruloplasmin may be within normal ranges, particularly early on, and so they do not completely exclude the diagnosis; enzymatic caeruloplasmin assays are better than immunological tests.
- We advise involving an ophthalmologist early to assess for Kayser–Fleischer rings with a slit lamp, and seeking advice from a liver specialist.
- Laboratory results correlate with the clinical symptoms; if there is doubt, then consider a 24-h urinary copper, liver function tests and, if necessary, liver biopsy or genetic testing.
- Scoring systems are a more reliable tool than individual tests in diagnosing Wilson’s disease.
to minimise its interference with pyridoxine action. Clinical improvement may occur after 2–6 months in those with symptomatic liver disease and after up to 3 years in patients with neurological features. In all, 10%–50% of patients experience worsening of neurological symptoms when starting D-penicillamine treatment. Other side effects include nephrotoxicity, bone marrow suppression and a lupus-like syndrome.

Trientene, developed for those intolerant to D-penicillamine, is also an effective initial treatment with fewer adverse effects. However, because it is an iron chelator, patients must avoid co-prescription of iron. A 24-h urinary copper excretion can assess the effectiveness of both D-penicillamine and trientine.

Ammonium tetrathiomolybdate, zinc and various antioxidants may potentially help in Wilson’s disease, but there is sparse evidence to support them. People with advanced disease may need liver transplantation because of severe cirrhosis or hepatic failure.

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