An unusual case of pyrexia of unknown origin with cervical lymphadenopathy

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Abstract
Kikuchi's disease is usually a self limiting illness characterised by pyrexia, neutropenia, and cervical lymphadenopathy particularly in young women of Asian descent. This often leads to an initial misdiagnosis of lymphoma. A case of a young Asian woman who presented with pyrexia of unknown origin is described. (Postgrad Med J 2000;76:655–656)

Keywords: pyrexia of unknown origin; cervical lymphadenopathy

Case report
A 19 year old south Asian women was admitted with a six week history of fever, malaise, anorexia, and cervical lymphadenopathy. She had been well until onset of her current illness. She was on no medication and had no contacts with tuberculosis.

She was born in India but had moved to the UK at the age of 9 years. Foreign travel included a brief return to her native country 10 years previously and a trip to the United States two years before presentation.

Clinical examination revealed a young woman who appeared well; her temperature was 39°C. The main findings were several tender mobile posterior cervical lymph nodes of which one was large. There were no lymph nodes elsewhere and she had no splenomegaly. The rest of the clinical examination was unremarkable.

Investigations revealed a low white cell count at 2.7 × 10^9/l with a neutrophil count of 1.3 × 10^9/l, a raised plasma viscosity of 1.99 cp (normal range 1.5–1.72). A biochemical profile, chest radiography, and abdominal ultrasound gave normal results.

The clinical impression was that this was likely to be tuberculous as she was Asian, or it could possibly be a lymphoma. Her clinical course was of a swinging intermittent pyrexia of up to 40.5°C. Blood and urine cultures, thin and thick films for malaria parasites, cytomegalovirus, Epstein-Barr virus, and HIV titres were all negative.

Tests for antinuclear factor, double stranded DNA, and antineutrophil cytoplasmic antibodies were negative. Thyroid microsomal antibody titres were positive at 1/400 and T cell analysis showed severe T lymphopenia of CD4, CD8, and NK populations with T cell activation. Later in her illness she had computed tomography of her chest, abdomen, and pelvis which was unremarkable, although minimal splenic enlargement was noted. Bone marrow aspiration and a trephine biopsy did not show any evidence of lymphoma or non-caseating granulomas.

The large posterior cervical lymph node was excised. Microscopic examination using an antibody against CD 68 showed numerous darkly staining histiocytes, many of them containing cell fragments. There was necrosis and apoptosis and immature lymphoid cells in keeping with a diagnosis of Kikuchi’s disease. Kikuchi’s disease was originally described in the Far East in 1972 and over the last decade has become increasingly recognised in the Western world.

Antibiotic treatment was withdrawn. Her temperature settled after three weeks, but she continued to remain neutropenic for six weeks from the beginning of the illness. When reviewed in outpatients four weeks after discharge from hospital she was well and all her lymph nodes had disappeared.

Discussion
The combination of pyrexia, neutropenia, and cervical lymphadenopathy particularly in young Asian women often leads to an initially wrong diagnosis of tuberculosis or even lymphoma. A massive release of cytokines, particularly interferon gamma and tumour necrosis factor, account for these symptoms and the necrosis.

Associations with systemic lupus erythmatosis and other autoimmune disorders (mixed connective tissue disease, Hashimoto’s thyroiditis) have been proposed. There is also anecdotal evidence of postviral disease. The disease is self limiting with a good prognosis and most patients appear to recover within a few weeks without any serious sequelae.

Learning points
- Kikuchi’s disease should be considered in patients presenting with pyrexia, neutropenia, and cervical lymphadenopathy
- It usually affects young female Asian patients
- The disease is self limiting with a good prognosis and most patients appear to recover within a few weeks without any serious sequelae
entity as far as general physicians in the UK are concerned. This was borne out by a straw poll of physicians in this hospital who were not aware of this condition clinically. There have been few reports of Kikuchi’s disease occurring in the UK, to our knowledge none by a general physician. This hopefully will make people, particularly where there is a large Asian population such as in Leicester, more aware of this benign condition which is readily diagnosed on lymph node biopsy.

Carotid sinus syndrome masquerading as treatment resistant epilepsy

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Abstract

A 65 year old woman had a 12 year history of frequent, recurrent seizure-like episodes labelled as treatment resistant epilepsy after neurological evaluation and follow up and treatment with multiple antiepileptic medications. Carotid sinus massage provoked 5.6 seconds asystole with symptom reproduction, and she has remained symptom-free after permanent pacemaker implantation for her carotid sinus syndrome and withdrawal of antiepileptic medications.

(Keywords: syncope; carotid sinus; pacing, artificial; epilepsy)

Carotid sinus syndrome (CSS) was previously thought to be a relatively rare cause of syncope and presyncope in older subjects, but recent work has shown that the syndrome is more common than was previously thought, accounting for up to 20% of permanent pacemaker implants in centres with an interest in the condition. The diagnosis rests on the finding of more than three seconds cardiac asystole (cardioinhibitory subtype), 50 mm Hg fall in systolic blood pressure (vasodepressor subtype), or both (mixed subtype) during carotid sinus massage in association with symptoms of presyncope or syncope. Permanent cardiac pacing for the cardioinhibitory and mixed subtypes provides dramatic relief of symptoms, resulting in grand mal seizures, sodium valproate, and carbamazepine with no improvement. The last three were eventually discontinued, and clonazepam and lamotrigine substituted with still no ease in symptoms. Over two episodes during a flight, she was referred to our facility.

Additional medical history was of hypertension, and current medications included clonazepam, phenytoin, enalapril, and bendrofluazide. Examination, 12 lead surface and 24 hour ambulatory electrocardiographs, 40 minute head-up tilt test and initial carotid sinus massage were unremarkable. There was no evidence of orthostatic hypotension, and 24 hour ambulatory blood pressure monitoring showed a mean of 138/74 mm Hg on antihypertensives. Repeat carotid sinus massage in the head-up tilt position resulted in 5.6 seconds cardiac asystole, with a 102 mm Hg fall in systolic blood pressure, loss of consciousness lasting a few minutes, with a variable prodrome of light headedness and prompt full recovery, though often with headache and nausea for up to several hours afterwards. She had experienced urinary incontinence during one of these episodes. Several had resulted in injury, including a fall from a ladder with loss of consciousness due to the head injury sustained. The patient was otherwise well and there were no witness accounts of the “fits”. She was referred for specialist neurological assessment, during which clinical examination was normal, electroencephalography (EEG) on three occasions, including 24 hour ambulatory EEG, showed no diagnostic features and computed tomography of the head was unremarkable. The diagnosis of partial complex seizures was made, and over the succeeding 12 years, was treated with varying combinations of phenytoin (which caused symptomatic toxicity on two occasions, one resulting in grand mal seizures), sodium valproate, and carbamazepine with no improvement. The last three were eventually discontinued, and clonazepam and lamotrigine substituted with still no ease in symptoms. After two episodes during a flight, she was referred to our facility.

References

reproduction of usual symptoms. The patient was referred for permanent pacemaker implantation, and has remained symptom-free during the ensuing one year follow up period. After a 12 year gap, the patient has now also returned to driving. Antiepileptics were withdrawn gradually, with no recurrence of symptoms.

Discussion
While other neurocardiovascular disorders, in particular vasovagal syncope, have been misdiagnosed as epilepsy previously, this is the first reported instance of CSS masquerading as an epileptiform disorder. In this case, our patient endured 12 years of frequent episodes of loss of consciousness, which severely impacted on her quality of life and deprived her of the ability to drive, as well as the marked adverse effects of over-medication. While the history was not characteristic of epilepsy, the combination of urinary incontinence and lack of a witness account conspired to direct the original diagnosis inappropriately. Unfortunately, alternative causes of syncope had not been entertained until late in this woman’s illness.

CSS should be considered in all subjects with unexplained syncope, in particular where loss of consciousness is short lived, with little or no prodrome and prompt recovery. As in this case, the “classic” CSS history of syncope associated with head turning and tight collars is by no means essential; on the contrary, the majority of patients with CSS give no such history, often presenting with unexplained syncope, drop attacks, and falls. If carotid sinus massage is initially negative, repeat massage in the upright position may provide a diagnosis in over 30% of cases where initial supine carotid sinus massage is negative.

Where seizure-like symptoms persist in a subject with poorly controlled epilepsy despite maximal antiepileptic therapy, particularly in the face of normal EEG, diagnostic re-evaluation for potential underlying cardiovascular disorders, in particular CSS, is mandatory.

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Learning points
- Cardiovascular syncope may present as a convulsive disorder
- Carotid sinus syndrome is more common than is generally appreciated and should be considered in all older patients presenting with loss of consciousness
- A witness account is important in formulating a differential diagnosis
- A label of “treatment resistance” should prompt full reappraisal of symptoms and diagnosis

Chorea disclosing deterioration of polycythemia vera

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Abstract
Neurological manifestations occur frequently in polycythemia. Chorea, however, is a rare complication of the disease. A case of chorea in a patient previously diagnosed with polycythemia vera is reported. Choreic movements started after measurement of haematological variables showed deterioration. It was considered that this was caused by inappropriate treatment with iron because the chorea was markedly reduced after the two first venesections and normalisation of the packed cell volume and haemoglobin parameters. (Postgrad Med J 2000;76:658–659)

Keywords: chorea; polycythemia vera

Polycythemia has gained the dubious distinction of being a haematological disorder with an inordinately high occurrence of neurological complications, which range from migrainous headaches and vertigo to much rarer complications such as extrapyramidal syndromes. Among the latter, chorea has been reported most frequently. The pathogenesis of polycythemic chorea still is a subject of speculation. We present a patient in whom chorea was the presenting symptom of a deterioration of the myeloproliferative disorder.

Case report
A 74 year old woman was admitted to hospital for investigation of involuntary movements involving the face, trunk, and limbs that had suddenly developed four days earlier.

General examination showed facial erythrosis but no splenomegaly. Blood pressure was 150/70 mm Hg and temperature was 36.5 ºC. The patient presented choreic movements involving limbs, trunk, and the orofaciolingual muscles with writhing movements of the tongue, grimacing, grunting, and a moderately severe dysarthria. There were marked choreic movements to the trunk leading to a lurching gait. Choreic movements were extremely violent so that restraint was required to prevent injury. The limbs were hypotonic with diminution of tendon reflexes. Her mental status was normal and neurological examination showed no other abnormality. The fundi were normal.

The patient had been diagnosed with a myeloproliferative disorder, polycythemia vera, 10 years before and she had regular haematology follow up. Her general practitioner started treatment with iron two months before.

There was no family history of chorea or dementia and she was not being treated with chorea inducing drugs.

Laboratory investigations confirmed the diagnosis of polycythemia according to current Polycythemia Vera Study Group guidelines. Before iron treatment her red blood cells were $6.43 \times 10^{12}/l$, haemoglobin concentration 117 g/l, packed cell volume 0.46, and platelet count 552 $\times 10^{9}/l$. At the onset of the choreic syndrome red blood cells were $7.60 \times 10^{12}/l$, haemoglobin 168 g/l, packed cell volume 0.64%, red cell volume 48.4 ml/kg (predicted normal 26.7 ml/kg), mean corpuscular volume 84.6 fl, white cell count $25 \times 10^{9}/l$, and platelets 474 $\times 10^{9}/l$. Her oxygen saturation was 90%, leucocyte alkaline phosphatase 366 U/l, vitamin B12 1770 pmol/l (reference range 150–700 pmol/l), and iron 4.8 µmol/l (reference range 6.6–32.2 µmol/l). Bone marrow examination showed global hyperplasia without fibrosis. Serum erythropoietin was <4 mU/ml (normal 5–20). Results of the following investigations were normal: uric acid and calcium concentrations, liver and thyroid function tests, tests for syphilis, HIV and chest radiograph, cerebrospinal fluid parameters, and cranial magnetic resonance imaging.

After four venesections (about 250 ml each) the choreic movements were markedly reduced and slight residual chorea was controlled with oral haloperidol 3 mg/24 hours. Haloperidol was progressively withdrawn and stopped in three weeks without chorea reappearing.

Improvement in the clinical picture was simultaneous with normalisation of haemoglobin and packed cell volume.

Discussion
Neurological manifestations of polycythemia vera occur frequently (50%–78%) and include headache, vertigo, stroke, visual symptoms, tinnitus, and paraesthesia. Chorea, however, is a rare and infrequently reported complication of the disease (0.5%–5%).

There is a clear relationship between the onset of chorea and haematological values worsening in the patient reported (probably caused by inappropriate iron treatment). Before iron treatment her packed cell volume was 0.46 and haemoglobin 117 g/l and at the onset of the polycythaemic chorea 0.64 and 168 g/l, respectively. Polycythaemia and chorea improved rapidly with venesections and follow up showed no recurrence of polycythaemia or neurological symptoms.

Pathophysiology of chorea due to polycythemia is far from clear. Blood hyperviscosity reducing and impairing oxygen transport, particularly in the basal ganglia, probably plays an important part in the pathogenesis. The most important determinant of the viscosity of whole blood is the packed cell volume, and an inverse relationship can be shown between cerebral blood flow and packed cell volume. Platelet
Chorea disclosing deterioration of polycythaemia vera

The onset of a choreic syndrome in patients with polycythaemia can alert us about deterioration in the packed cell volume and haemoglobin values. Polycythaemia chorea must be considered because this diagnosis leads to effective treatment and prevention of serious complications—for example, deep vein thrombosis, pulmonary embolism, and stroke.

It is important to note that the onset of a choreic syndrome in patients with polycythaemia vera is more difficult to analyse because the packed cell volume has an apparently dominant role. The relative stiffness of iron deficient red cells could influence in the pathophysiology of chorea. It has been inferred from viscometric studies that red blood cell deformability might be reduced in iron deficiency, and the effect of iron deficient red cell changes on whole blood viscosity has been assessed at a wide range of standardised packed cell volumes. The female preponderance (post-menopausal oestrogen deficit) and an underlying individual predisposition had also been discussed.

Most cases of polycythaemia chorea have occurred in elderly women, usually with acute onset or sudden aggravation. In some cases chorea is the presenting symptom of polycythaemia vera. The choreic syndrome is usually generalised with predominant involvement of the orofaciolingual muscles, but it might be unilateral.

Learning points

- Headache: 41%
- Dizziness or vertigo: 30%
- Paresthesias: 13%
- Visual: 11%
- Stroke: 9%
- Tinnitus: 3%
- Extrapyramidal syndromes: 0.5%–2.5%

Box 1: Neurological complications in patients with polycythaemia

- Headache
- Dizziness or vertigo
- Paresthesias
- Visual
- Stroke
- Tinnitus
- Extrapyramidal syndromes

Box 2: Learning points

- The onset of a choreic syndrome in patients with polycythaemia can alert us about deterioration in the packed cell volume and haemoglobin values.
- Polycythaemia chorea must be considered because this diagnosis leads to effective treatment and prevention of serious complications—for example, deep vein thrombosis, pulmonary embolism, and stroke.

Box 3: Possible causes of chorea

- Developmental and aging choras: physiological chorea of infancy; cerebral palsy-anoxic; kernicterus; minimal cerebral dysfunction; buccal-oral-lingual dyskinesia and edentulous orodyskinesia; senile chorea.
- Hereditary choras: Huntington’s disease; benign hereditary chorea; neuroacanthocytosis; olivopontocerebellar atrophy; Machado-Joseph disease; ataxia telangiectasia; tuberosus sclerosis; Hallervorden-Spatz disease; Friedreich’s ataxia; familial calcification of basal ganglia; neurometabolic disorders: Wilson’s disease, Lesch-Nyhan syndrome; lysosomal storage disorders; amino acid disorders; Leigh’s disease; porphyria.
- Drug induced neuroleptics (tardive dyskinesia): antiparkinsonian drugs; amphetamines; cocaine; tricyclic; oral contraceptives.
- Toxins and alcohol intoxication and withdrawal: anoxia; carbon monoxide; manganese; mercury; thallium; toluene.
- Metabolic: hyperthyroidism; hypoparathyroidism; chorea gravidarum; hypernatraemia and hyponatraemia; hypomagnesaeemia; hypocalcaemia; hypoglycaemia and hyperglycaemia; acquired hepatocerebral degeneration; nutritional (for example, beriberi, pellagra, vitamin B deficiency in infants).
- Infectious: Sydenham’s chorea; encephalitis lethargica; various other infectious and postinfectious encephalitides, including Creutzfeldt-Jakob disease.
- Immunological: systemic lupus erythematosus; Henoch-Schönlein purpura; others (rarely): sarcoidosis, multiple sclerosis, Behçet’s disease, polyarteritis nodosa.
- Vascular: infarction; haemorrhage; arteriovenous malformation; moyamoya disease; polycythaemia vera; migraine.
- Tumours.
- Trauma: including subdural and epidural haematoma.
- Miscellaneous: including paroxysmal choreoathetosis.