The danger of ignoring a migraine

Q1: What is the term used to describe the MRI brain appearance in fig 1 (see p 53)?
Reversible posterior leucoencephalopathy syndrome (RPLS).

Q2: Give the underlying cause of the brain appearance in this case
Hypertension.

Q3: Give three other causes of this condition
These are:
(1) Drug induced reports of association with cisplatin, cyclosporin, tacrolimus, and intravenous immunoglobulin.
(2) Associated with eclampsia.
(3) Associated with thrombotic thrombocytopenic purpura.

Q4: What is the likely cause of the fundal appearance in fig 1 (see p 53)?
Hypertensive retinopathy.

Q5: What other investigations would you order?
Urinal vanillylmandelic acid measurement and ultrasound of the abdomen to exclude renal artery stenosis or a renal/adrenal mass.

Discussion
Reversible changes of the white matter on computed tomography of the brain in hypertensive encephalopathy have been recognised for some time, but the term RPLS was first coined by Hinchey and colleagues in 1996. The condition is also seen secondary to the toxoaemia of pregnancy, thrombotic thrombocytopenic purpura, or after the use of some immunosuppressive or chemotherapeutic agents. The most common clinical symptoms recognised are headache, alteration of alertness, seizures, vomiting, and abnormally high, altered, or altered vision, hemianopia, visual neglect, and cortical blindness. Diagnosis in this case had been delayed as, being a lifelong migraineur, headache and visual loss (albeit transient in nature) were not unusual symptoms.

The commonest change on neuroimaging is oedema of the white matter primarily of the parieto-occipital lobes, although involvement of other areas of the brain and brainstem has also been reported. The pathogenesis is thought to involve areas of cerebral focal vasodilatation and vasoconstriction due to sudden elevation of arterial blood pressure exceeding the autoregulatory capacity of the brain vasculature. This ultimately results in breakdown of the blood-brain barrier and fluid transudation most marked in highly myelinated areas.

In the context of this case, it is worth noting the association of migraine with stroke. Migraine headache can be an independent risk factor for stroke (risk of ischaemic stroke can be increased threefold in migraineur European females of childbearing age) or occur in association with genetic syndromes causing stroke (for example, MELAS [mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes], familial hemiplegic migraine and CADASIL [cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy]). Migraine, as well as tension headache, can also occur secondary to ischaemic or haemorrhagic stroke (especially in the context of a posterior circulation event). In the case history described here, the absence of a homonymous hemianopia type field defect and, in addition, neuroimaging evidence of bilateral hemispheric involvement, would make either of these two migrainous entities unlikely.

This case illustrates the importance of fundoscopy and blood pressure measurement in all cases of headache, including those with a typical history of migraine, and furthermore highlights the complex association between migraine and intracerebral vascular events.

Final diagnosis
Reversible posterior leucoencephalopathy syndrome.

References

Hyperkalaemia in an elderly diabetic patient

Q1: What are the factors causing his hyperkalaemia?
The factors contributing to his hyperkalaemia were:
• Increased dietary intake of potassium (both coffee and orange juice have a proportionately high potassium content).
• Age related deterioration in renal function.
• Hyporeninaemic hypoaldosteronism. This disorder is commonly seen in mild renal insufficiency, diabetic nephropathy, or tubulointerstitial disease. It is usually confined to older age groups and is characterised by euveolaemia or extracellular fluid volume expansion and suppressed renin and aldosterone levels. Enhanced distal chloride reabsorption may account for many of the biochemical findings, while impaired conversion of prorenin to renin and prostaglandin deficiency are contributory factors. The hyperkalaemia caused by this condition is generally mild in the absence of increased potassium intake or renal dysfunction.
• Nebivolol: this is a β-receptor specific blocking agent. β-Adrenergic blockade impairs extrarenal disposal of potassium load. Increased cellular uptake of potassium appears to be β-receptor specific, with the cellular mechanism involving stimulation of cyclic AMP followed by activation of Na+-K+ ATPase.

Q2: Why are elderly patients prone to developing hyperkalaemia?
Elderly patients are more prone to developing hyperkalaemia because of:
• A gradual reduction in glomerular filtration rate and renal blood flow.
• A decline in distal renal tubular function, which in turn causes a reduction in potassium secretion.
• Impairment in tubular response to acidosis.
• Declining levels of both renin and aldosterone.
• Reduced sensitivity of the distal convoluted tubule to aldosterone.
• An ageing associated increase in atrial natriuretic factor, which is a powerful suppressor of aldosterone secretion.

Q3: How would you manage this patient?
In the acute situation he was managed with a glucose/insulin infusion after providing cardiac protection with intravenous calcium gluconate. He was then started on a short course of oral calcium resonium. Subsequently at discharge, he was started on a low potassium diet and nebivolol was replaced by amiodipine. His serum potassium at the outpatient clinic four months later was 4.8 mmol/l.

References

Recurrent orogenital ulcers with papilloedema and headaches

Q1: What is the initial diagnosis?
Behcet’s syndrome.

Q2: What does the unenhanced computed tomogram of the brain show (see p 54)?
This is a normal unenhanced computed tomogram of the brain.

Q3: What probable complication of the initial diagnosis has occurred?
Dural sinus thrombosis.

Q4: What further investigation will you do to confirm the complication?
Magnetic resonance imaging venogram or computed tomogram of the brain with contrast.

Q5: What is the treatment of this complication?
Anticoagulation with heparin and warfarin.

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MRI; fig 1) and MRI venogram lar malformation, and benign intracranial accident, intracranial neoplasm, vascular sinus thrombosis includes cerebrovascular present. The clinical differential diagnosis for symptoms, such as headache, nausea and the reaction is specific for Behçet's disease. Hyper-reactive lesion (papulopustular) at the where the venous drainage of the brain was formation, occurring in about 36% of patients. Segment complication after recurrent inflammation. Other ocular presentations include episcleritis, scleritis, retinal vein thrombosis, and migratory thrombophlebitis. Recurrent anterior uveitis with hypopyon formation and, less frequently, retinal vasculitis are the main manifestations in the ocular involvement of Behçet's disease. Other ocular presentations include episcleritis, scleritis, retinal vein thrombosis, and corneal and conjunctival ulcers. Cataract formation is the most common anterior segment complication after recurrent inflammation, occurring in about 36% of patients. Other systems can be involved, primarily due to the thrombotic and vaso-occlusive changes affecting vessels of all sizes, as in our case where the venous drainage of the brain was affected causing dural sinus thrombosis. The skin pathergy reaction is a non-specific, hyper-reactive lesion (papulopustular) at the site of trauma or a needle prick. When present the reaction is specific for Behçet's disease. Dural sinus thrombosis may be acute or chronic and may present with non-specific symptoms, such as headache, nausea and vomiting, altered mental status, and seizures. Focal neurological complaints may also be present. The clinical differential diagnosis for dural sinus thrombosis includes cerebrovascular accident, intracranial neoplasm, vascular malformation, and benign intracranial hypertension. Magnetic resonance imaging (MRI; fig 1) and MRI venogram or computed tomography of the brain with contrast are valuable in diagnosing dural sinus thrombosis. Unenhanced computed tomography of the brain is less sensitive in delineating a sinus thrombosis and may appear falsely negative. Treatment of dural sinus thrombosis is usually anticoagulation with heparin and warfarin. Local infusion of urokinase, a thrombolytic agent, is being tried and holds promise.

Final diagnosis
Behçet's syndrome with dural sinus thrombosis as a complication.

References

Malaise, weight loss, and respiratory symptoms
Q1: What abnormalities are shown in the flow volume loops?
Restrictive lung defect with reduced lung volumes, plus minor airflow obstruction.
Q2: What abnormalities are shown in the chest radiograph and computed tomogram (see p 55)?
The chest radiograph shows bilateral interstitial infiltrate in the lung with loss of lung volume. HRCT shows ground glass opacification in the mid thoracic region with patchy fibrosis and traction bronchiectasis.
Q3: What is the differential diagnosis?
(A) Drug induced alveolitis.
(B) Cryptogenic fibrosing alveolitis.
(C) Extrinsic allergic alveolitis.
Outcome
The patient had been taking prophylactic nitrofurantoin 100 mg daily for the preceding 11 months because of recurrent urinary tract infections. This antibiotic was stopped two days after her presentation and the patient was then treated with oral steroids. Her condition improved significantly within one month, allowing a gradual reduction in steroid dosage thereafter. Three months later, by which time the steroids had been discontinued, a control chest radiograph (fig 1, above) showed complete resolution of the lower zone infiltrate.

Discussion
The combination of progressive dyspnoea and cough, with audible crackles on auscultation of the lungs, and the chest radiograph appearances of an interstitial infiltrate, should suggest a diagnosis of fibrosing alveolitis. Whereas the epithet “cryptogenic” can reasonably be applied to the majority of such cases where a specific causal factor cannot be identified, it is important to consider potential aetiological factors. Though uncommon, the recognition and removal of such agents can result in significant clinical improvement. Nitrofurantoin is one of many drugs that can be implicated (box 1). Extrinsic allergic alveolitis (for example, bird fancier’s lung) can also present with a similar picture.

Nitrofurantoin is widely used in treating acute urinary tract infections and in suppression of chronic asymptomatic bacteruria. It was one of the first drugs to be implicated as a cause of pulmonary disease and is associated with various toxic pulmonary manifestations (box 2). Nitrofurantoin induced pulmonary disease is postulated to result from the
generation of free radicals as a result of redox cycling of the drug in the lung causing direct tissue damage to the endothelium and the alveoli. Antioxidant depleted tissues are most vulnerable.1

Classically, the pulmonary reaction to nitrofurantoin is divided into acute and chronic forms, though some authorities are suggesting a wide spectrum because of the heterogeneity of manifestations.5 The acute form begins hours to several days after the initiation of therapy. Symptoms include fever, dyspnoea, bronchospasm, rash, arthralgia, and pleural pain. Eosinophilic leukocytosis, high ESR, pleural effusions, and an intermittent infiltrate on chest radiography are common findings. Management entails discontinuation of the medication and supportive measures. While the role of steroids is unclear, they are often prescribed.18,19

The chronic form of reaction is less common, and fever and eosinophilia occur less frequently. It usually affects older females and occurs many months or years after initiation of treatment. The onset of cough and dyspnoea is usually insidious and is commonly accompanied by constitutional symptoms of fatigue and weight loss. Chest radiographs show a diffuse interstitial process. HRCT is particularly helpful in outlining the extent of pulmonary injury and evaluating disease activity. Desquamative pneumonitis and ground-glass opacification is usually associated with a good prognosis and is radiologically reversible, while a reticular pattern implies irregular fibrosis and is usually irreversible.20 Pulmonary function tests demonstrate a restrictive pattern with a reduced diffusion capacity. A positive rheumatoid factor, antinuclear antibodies, and raised immunoglobulin levels may be associated features.

Bronchoalveolar lavage shows a lymphocytic reaction while histology shows inflammation and interstitial fibrosis, though the appearances are somewhat non-specific. Immediate cessation of nitrofurantoin treatment is essential, but the role of steroids is uncertain. While steroids might be justified in the presence of a pulmonary infiltrate, desquamative pneumonitis or bronchiolitis obliterans organising pneumonia, they are unlikely to be effective for established fibrosis.20 The outcome tends to be less favourable in the chronic disease pattern, which has a mortality of 8% and in which 75% of cases fail to resolve fully.1

The relevance and importance of this patient’s medication history was not fully realised at the time of presentation. A detailed drug history should always be sought and the possibility of a drug induced illness considered in the differential diagnosis.

The incidence of HAV shows a cyclical pattern in the UK, the most recent peak year being 1992 when 7856 cases in England and Wales were reported to the Public Health Laboratory Service. In 1999, there were 1676 cases reported.11

Q2: What was the diagnostic test performed?

The diagnosis is established by detecting the presence of serum IgM antibody to the capsid proteins of HAV. These usually become detectable 5–10 days before the onset of symptoms. IgG anti-HAV, which appears after several weeks of infection, persists for lifelong immunity against the disease.

Q3: What are the risk factors for contracting this condition?

HAV is acquired primarily by the faeco-oral route by either person-to-person contact or ingestion of contaminated food or water. In developing countries, water borne and food borne transmission is almost universal in childhood and responsible for HAV endemicity. However, in areas of low prevalence, extensive outbreaks may occur, for example, in South Africa in 1988 in which 70–800000 cases was linked to consumption of infected clams.24

Improved sanitation in developed countries has dramatically reduced the incidence of HAV over the last 25 years; however, this leaves many adults susceptible to HAV infection. In developed countries, the most frequent source of HAV infection during community outbreaks is from personal or household transmission between household and sexual contacts, accounting for 12%–26% of cases.25 As most children have asymptomatic or unrecognized infection, the non-immune population is the most important part in HAV transmission and acts as a source of infection for others, for example in day care centres and close communities.26

Travellers to countries that have high endemicity of hepatitis A are at substantial risk of acquiring HAV. In 1999, 60% of the notified cases in England and Wales included a history of travel abroad before the onset of illness.27

Proactive studies suggest that the risk to non-immune travellers is 3–5/1000 per month of stay.28

Hepatitis A outbreaks have been identified in homosexual men with association noted between oral-anal contact, the incidence of other sexually transmitted diseases, and multiple partners. Intravenous drug users have higher anti-HAV seropositivity than the general population and outbreaks have been reported in these communities.11

Several outbreaks of HAV have been reported in the United States and Europe among patients with clotting factors disorders receiving solvent-detergent-treated factor VIII and IX concentrates contaminated from plasma donors incubating HAV. Although not at increased risk of contracting HAV, those who have chronic liver disease are at increased risk of fulminant hepatitis A and should be considered for immunisation.

Box 2: Toxic pulmonary manifestation of nitrofurantoin

- Hypersensitivitiy pneumonitis.
- Interstitial fibrosis.
- Pulmonary eosinophilia.
- Bronchiolitis obliterans organising pneumonia.
- Pulmonary vasculitis.
- Pleural disease.
- Airway disease.
- Desquamative interstitial pneumonia.
- Adult respiratory distress syndrome.
- Pulmonary haemosiderosis.

Jaundice in primary school pupils

Q1: What is the likely and differential diagnosis?

The liver function abnormalities in the teacher reveal a marked increase of ALT suggesting acute hepaticellular damage. There are a wide range of causes of acute hepatitis (see box 1).

Assuming that the boy had the same illness, the most likely cause in this setting is infective viral hepatitis A (HAV). HAV is an RNA hepatitisvirus belonging to the family picornaviridae. HAV is an enteric infection and has a mean incubation period of 28 days (range 15–50). The likelihood of developing symptomatic infection is related to the patient’s age. Children less than 6 years old, 70%–90% of infections are asymptomatic, and if illness does occur, it is usually mild.2

In adults, infection is usually symptomatic and variable in clinical severity, with jaundice occurring in over 70% patients affected.7 Convalescence may be prolonged over several months, but there is usually complete recovery. There was no direct contact between the teacher and school child and it is therefore likely that infection was acquired as part of an outbreak rather than by person-to-person transmission.

Box 1: Causes of acute hepatitis

- Bacterial infection: leptospirosis, tuberculosis, alcohol.
- Liver hyperperfusion and hypoxia.
- Drug induced: antibiotics, oral contraceptive pill, phenothiazines.
- Toxins: carbon tetrachloride, solvents.
- Metabolic: Wilson’s disease, haemochromatosis.
- Autoimmune: chronic active, lupoid.

Final diagnosis

Drug induced alveolitis.

References

Box 2: People at risk for HAV

- Household or sexual partners of patient.
- Those with poor sanitation and exposed to raw sewage.
- Those exposed to water borne or food contamination—for example, shellfish.
- Travellers to endemic areas.
- Homosexual men.
- Intravenous drug users.
- Recipients of factor VIII and IX concentrate.
- Laboratory workers in direct contact with HAV.
- Residents of institutions for the mentally handicapped.
- Young children and staff in nurseries.

susceptible to infection has risen. Adults are more likely to have severe illness, which increases the importance of controlling outbreaks. There are several vaccination strategies that can be used for control of outbreaks and post-exposure prophylaxis.

The current recommendation in the UK Department of Health Handbook is to provide protection through the passive transfer of antibody by use of human normal immunoglobulin (HNIG). When administered within two weeks after an exposure to HAV, HNIG has protective efficacy of over 85%. However, this strategy poses a number of concerns. HNIG is administered by deep muscular injection that can be painful, limiting its use in children and mass campaigns. It may interfere with the development of active immunity from live vaccines such as measles, mumps, and rubella. Although plasma donors are tested for blood borne viruses, there is general concern regarding the use of human blood products and the potential risk of transmissible spongiform encephalopathies.

Hepatitis A vaccine is easier to administer and, after a booster, offers up to 10 years of protection that can be used in populations with low natural immunity. It does not interfere with the immunogenicity of other vaccines. Double blind, placebo controlled studies suggest protective antibody response of between 94% and 100% at four weeks after immunisation. In one study, over 90% sero-negative vaccines developed protective IgG three to four weeks after single dose immunisation.

Several studies have confirmed the effectiveness of HAV vaccine without HNIG in controlling outbreaks. In populations of high HAV endemicity, inactivated vaccine has been successfully used to terminate ongoing established epidemics. There has been successful use of HAV vaccine in the control of community outbreaks in schools and day centres. Although the incubation of HAV infection may be up to 50 days, a randomised controlled trial of HAV vaccine found that it was 79% efficacious in preventing development of HAV IgM positivity after post-household exposure compared with no treatment. No cases of HAV in vaccine recipients were reported during use of inactivated hepatitis A vaccine to terminate an outbreak. Furthermore, in chimpanzee animal models, inactivated HAV vaccine can prevent infection if given shortly after HAV exposure therefore suggesting a post-exposure prophylaxis effect in those already infected. In practice, however, there remains the risk that those already infected at the time of immunoprophylaxis will develop symptomatic illness, although this risk appears less with inactivated vaccine than with passive immunity by administration of HNIG. There have been no clinical trials of HNIG compared with inactivated HAV vaccine in prevention of HAV.

Several vaccination approaches have been used, including protecting adults alone in small outbreaks (as those most susceptible to serious illness), both adults and children, extending vaccination to household contacts or targeting those at risk by identifying serological status by measurement of salivary IgM and IgG anti-HAV.

Final diagnosis

Acute HAV outbreak managed by immunisation of all adults in school and household contacts of both cases.

References

3. PHLS Facts and Figures. Hepatitis A. [www.phls.co.uk].