Progressive multifocal leukoencephalopathy – a rare but serious disease

Immunomodulatory medicines have emerged as a class of medicines associated with the development of progressive multifocal leukoencephalopathy.

Awareness of risk factors and early recognition of symptoms is important as early diagnosis is likely to improve the prognosis.

What is PML?
Progressive multifocal leukoencephalopathy (PML) is a rare, but often fatal, demyelinating disease of the central nervous system. PML is caused by lytic infection of oligodendrocytes and astrocytes resulting in multiple areas of demyelination in the central nervous system.

PML lesions are typically asymmetrical demyelinated plaque areas with irregular borders, surrounded by macrophages and irregular astrocytes with large, multiple nuclei. On magnetic resonance imaging (MRI), the lesions usually do not show oedema, mass effect or gadolinium enhancement, which are common in multiple sclerosis.

Patients with PML can have a variety of symptoms including muscle weakness, sensory deficit, cognitive dysfunction, language impairment and/or coordination and gait difficulties.

What causes PML?
PML is caused by a human polyomavirus, the JC virus. The virus was named after the patient from whom it was initially cultivated, John Cunningham. Approximately 50% of the world’s population are infected with the virus by the time they reach age 20, although most remain asymptomatic. After initial virus infection, the virus remains quiescent in the kidneys, bone marrow and lymphoid tissue.

In immunocompromised individuals the quiescent virus can reactivate, enter the bloodstream and then gain entry to the central nervous system where it infects oligodendrocytes and astrocytes. Infection of these cells leads to cell death, and the resulting demyelination produces the neurological signs and symptoms of PML.

Viruses isolated from the brains of individuals with PML have a genomic rearrangement in the regulatory region that is not found in the strains responsible for initial infection.

What are the risk factors?
Patients who are immunosuppressed or have a malfunction of the immune system are at higher risk of developing PML. Cell-mediated immunity disorders are the major immunological disorders that predispose individuals to the development of PML.

PML cases have been reported in patients with HIV, lymphoproliferative disorders, malignancies, patients on immunosuppressive therapy after solid organ transplantation and in rheumatic diseases such as systemic lupus erythematosus.

Immunosuppressive medications that have been associated with PML include cyclophosphamide, corticosteroids, mycophenolate mofetil and monoclonal antibodies including natalizumab (Tysabri), rituximab (Mabthera) and alemtuzumab (MabCampath). The Australian Product Information for both rituximab and natalizumab carries a black box warning on the risk of PML.
How is PML diagnosed?
Diagnosis should be considered in any patient with risk factors who presents with progressive neurological signs or symptoms and has MRI evidence of multiple characteristic lesions. The early signs of PML are often related to cognitive dysfunction, manifesting as mental slowness, disorientation and behavioural changes. Motor and sensory disturbance, characterised by lack of coordination, gait disturbance, ataxia, hemiparesis or visual deficits may also be found at the time of presentation. Seizures, language difficulties and headaches can occur but are less common. These signs and symptoms progress over the course of a few weeks and death can occur weeks to months after diagnosis.

The diagnosis can be confirmed by detection of JC virus DNA or proteins using in situ hybridisation or immunohistochemistry on a brain biopsy sample, or by detection of JC virus DNA in the cerebrospinal fluid by quantitative polymerase chain reaction. However, a negative polymerase chain reaction result does not exclude the diagnosis of PML, particularly early in the disease.

How many cases have been reported?
A search of the Australian and New Zealand adverse event databases found 28 reports of PML (Table). Many of these cases had multiple risk factors including prior or concomitant immunosuppression therapies, underlying disease and chemotherapy. The majority of reports were associated with the monoclonal antibodies, rituximab and natalizumab. However, this may be due to greater awareness of PML in association with these particular medicines.

<table>
<thead>
<tr>
<th>Medicine</th>
<th>No. of reports</th>
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<tbody>
<tr>
<td>Rituximab*</td>
<td>13</td>
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<tr>
<td>Natalizumab</td>
<td>13</td>
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<tr>
<td>Alemtuzumab</td>
<td>1</td>
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<tr>
<td>Cyclophosphamide*</td>
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<td>Prednisolone*</td>
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<tr>
<td>Mycophenolate mofetil®</td>
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<tr>
<td>Tacrolimus®</td>
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<td>Dexamethasone®</td>
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* Co-suspect medicines in same report

How is PML treated?
Improved chance of survival is associated with early diagnosis, younger age at diagnosis and if the disease is limited to one lobe of the brain. Current treatment of PML is limited and is generally supportive in nature.

The current treatment strategy for PML in HIV-negative patients is to restore the host adaptive immune response by stopping or decreasing immunosuppression. There are currently no specific antiviral drugs for the JC virus.

Recovery of the immune system can trigger immune reconstitution inflammatory syndrome (IRIS). In HIV-negative patients with PML-IRIS, the current treatment is corticosteroids to reduce the inflammatory response.

Key messages
- PML is a rare but potentially fatal disease
- Patients with compromised immune systems due to immunomodulatory medicines or disease are at risk of developing PML
- A diagnosis of PML should be considered for any patient with risk factors who presents with progressive neurological signs or symptoms
- Early diagnosis is associated with an improved chance of survival

Conjointly prepared by the TGA and Medsafe (the New Zealand Medicines and Medical Devices Safety Authority)

REFERENCES
Thyroxine (Eutroxsig and Oroxine) and fractures

Health professionals are advised that the Product Information for thyroxine has recently been updated to include a precaution about the increased risk of osteoporotic fracture associated with excessive thyroxine doses. Control of hypothyroidism should be monitored regularly, especially in the elderly, and the thyroxine dose adjusted accordingly.

Chronic hyperthyroidism promotes bone turnover, characterised by increases in bone resorption and in urinary excretion of calcium and phosphorus. Increased bone resorption may result in osteoporosis and an increased risk of fracture. A similar risk appears to exist for hypothyroid patients receiving higher-than-needed doses of thyroxine. The elderly may be at particularly increased risk, since thyroxine replacement needs decrease with age, and age is an additional risk factor for osteoporosis.1

Fracture risk with thyroxine replacement therapy

Two recent large studies have examined the risk of fracture in patients on long-term thyroxine replacement. A nested case-control study in 213 511 Canadian thyroxine users aged over 70 followed patients for a mean of 3.8 years.1 Thyroxine use was classified as high (>93 microgram), medium (44–93 microgram) or low dose (<44 microgram daily) based on cumulative dose over the preceding 12 months. Among current (at the time of fracture) thyroxine users, high thyroxine doses were associated with a 3.5-fold increased risk of fracture, and medium doses with a 2.6-fold increased risk, compared to low doses. Both these results were statistically significant. The study did not check for appropriateness of thyroxine use by measuring thyroid stimulating hormone (TSH) levels.

An observational cohort study in 17 684 Scottish thyroxine users aged 18 and over, with a median follow-up of 4.5 years, classified patients according to their mean TSH level over time, into suppressed (TSH ≤0.03 mU/L), low (0.04–0.4 mU/L), normal (0.4–4.0 mU/L) and high (>4.0 mU/L).2 Compared to patients with normal TSH, there was a statistically significant two-fold increased risk of hospitalisation or death due to osteoporotic fracture in patients with suppressed TSH. There was no significant increase in risk for patients with a low (but not suppressed) TSH.

Although neither study measured both thyroxine and TSH levels, each found an association between either high or excessive (as measured by TSH suppression) thyroxine dose and fracture. As well as increasing the risk of osteoporosis, excess thyroxine may also increase the risk of falls secondary to arrhythmia or muscle weakness, particularly in the elderly.

Information for health professionals

Health professionals are advised that the Product Information for thyroxine (Oroxine, Eutroxsig) has recently been updated with a new precaution about the effects of thyroxine on bone mineral density. It is recommended that patients receiving thyroxine are given the minimum dose necessary to achieve the desired clinical and biochemical response. Prescribers should keep in mind that replacement thyroxine needs decrease in the elderly and serum TSH should be monitored regularly and thyroxine doses adjusted accordingly. The risk of fracture may be greater in patients with other risk factors for osteoporosis, including postmenopausal women, those with a family history or past history of fracture or osteoporosis, smokers, and patients with vitamin D deficiency.

REFERENCES


Oral bowel cleansing products – serious electrolyte disturbances

The use of oral bowel cleansing products is part of the preparation for a number of medical, diagnostic and surgical procedures. These products create a cathartic effect by osmotic action, resulting in a transfer of fluid and electrolytes to the gut lumen. Marked dehydration, electrolyte abnormalities and associated complications may occur as a result in otherwise well patients. The TGA has previously alerted prescribers to the risk of severe electrolyte disturbances in association with the use of sodium picosulfate-containing products.1

Since January 2002 the TGA has received a total of 51 adverse event reports for these products, of which 18 were reports of serious electrolyte disturbances. One of these reports was of a 60-year-old patient who experienced a cardiac arrest, one was of a 50-year-old patient who sustained permanent hypoxic brain damage as a result of serious adverse events following hypotension, and a third report was of a 38-year-old who developed hypotensive encephalopathy. While it is known that the elderly, the frail and those with cardiac failure or renal impairment are potentially at higher risk of an adverse event, health professionals are reminded that serious adverse events can occur in patients under the age of 60 who are otherwise fit and healthy, and that this should be considered when prescribing/dispensing these products. All patients should be reminded of the importance of hydration and electrolyte replacement while taking these products and to seek medical attention if they experience any signs of severe dehydration, such as excessive thirst, dizziness, confusion and decreased urine output or dark coloured urine.

REFERENCE