PRIMARL ANGIIITIS OF THE CENTRAL NERVOUS SYSTEM

PACNS is a very rare disorder which probably affects less than 1 per million people. Its cause is poorly understood and the disease has been under-researched. Vasculitis is a disorder of blood vessels caused by inflammation within them, and so a cerebral vasculitis is a disorder of the brain caused by inflammation of the blood vessels within the brain. Angiitis is another term which describes the same process. There is a high chance that it is under-recognised and that delays in diagnosis lead to a poor response to treatment and residual neurological impairments. It may even be fatal.

An angiitis of the nervous system can arise within a systemic inflammatory disease, for example during infections (see table 1) and as a complication of connective tissue diseases such as lupus and arthritis, and systemic vasculitis. When it affects the brain it is a cerebral vasculitis or angiitis of the central nervous system, and when it affects the peripheral nerves a vasculitic neuropathy develops. This is much more common than a cerebral vasculitis.

Different subtypes

When there is an underlying cause for the disease it is known as secondary angiitis of the nervous system. These diseases usually have signs of a disease process elsewhere in the body which makes it easier to identify at an earlier point. The best treatment of the brain disease will be the same treatment for the inflammatory disease elsewhere in the body.

In a primary angiitis of the nervous system there are no signs of inflammation outside of the central nervous system. Patients develop headache then focal neurological symptoms which may come on suddenly, simulating stroke, or subacutely resembling an inflammatory disease. Many develop changes in memory and personality, and some have seizures. Others present with a gradually worsening disorder simulating a tumour. Patients can lose their sight and their hearing.

Symptoms

These symptoms can arise as a result of many different diseases processes, and cerebral vasculitis would never be top of the list of possible causes initially (because it is so rare). However it usually continues to worsen and if left untreated the disorder progresses, deteriorates and may become extremely severe.
Investigations
The blood tests are usually normal but an MRI of the brain is abnormal, with lesions often widespread throughout the brain, which mimic strokes, but which are smaller than those caused by cerebral artery occlusion leading to stroke, and more widespread. The lesions tend to be subcortical (near the surface of the brain) and so look different to other brain diseases such as multiple sclerosis. There may be evidence for meningeal enhancement, which is an important sign which shows up if an injection of contrast is given. Angiographic studies (arteriography, MRA or CTA), which are imaging tests of the blood vessels within the brain, are often normal but may show alternating narrowing and dilatation (beading), although this is not a specific feature of vasculitis and may occur in other non-vasculitic diseases, principally reversible cerebral vasoconstriction syndrome, and also intracranial infections and following radiotherapy. It is extremely important that a very careful assessment is made if beading is seen, since the treatment for these various and very different conditions is not the same.

The spinal fluid is usually active, with raised protein and cell count.

The only way of diagnosing the condition with certainty is to perform a brain biopsy. This obviously sounds worrying, but is carried out very carefully and only a very small sample is taken, with the result that the chance of something going wrong, such as bleeding or infection, is very low. The sample is then analysed in a neuropathology department where the brain tissue is examined and special staining tests can be carried out to make a correct diagnosis.

There are three subtypes:
1. Granulomatous angiitis
2. Lymphocytic angiitis
3. Angitis associated with β-amyloid

Each presents in a similar way; that associated with cerebral amyloid angiopathy occurs in an older age group. The granulomatous form is the more common of the other two, and probably more severe.

Treatment
It is not known yet which are the optimum treatments for each subtype; it is clear from individual reports that steroids and immunosuppression, particularly with cyclophosphamide, allows regression of the disease and a prevention of further neurological impairment, but with delays in diagnosis and an uncertainly about how aggressive the treatment should be, residual impairments and disability including epilepsy and cognitive dysfunction remain in the long term, and patients rarely are able to return to work, and require additional help and supervision at home.

Research
At the Neuroimmunology unit of the Institute of Immunity and Transplantation we are commencing a three year prospective research programme partly funded by Vasculitis UK in which we hope to identify all cases of PACNS diagnosed within the UK. We will be analysing the clinical features and imaging abnormalities and correlating with the CSF and histological appearances. We will be performing quantitative immunopathology analyses which we hope will identify subtypes amenable to certain more specific treatments, particularly biological agents, and thereby to increase our understanding of the disease and, most importantly of all, identify a clear and rapid diagnostic pathway and treatment algorithm. We are confident that this research will allow all Doctors to
identify the disease more quickly and to understand how to treat it more aggressively and at an earlier point, in order that patients have a much greater chance of recovery before the disease causes permanent harm.

Patients thought to have PACNS will be invited by their treating Doctors and through advertising through the vasculitis UK website and at (insert Royal Free website address) to permit us to examine their symptoms and neurological signs, their investigation results (blood tests, scans and lumbar puncture results) and, if it has been carried out, their brain biopsy tissue. We will be re-examining this tissue in order to identify patterns and to correlate with the clinical symptoms and severity, thereby to define further the most appropriate treatments for the disease and its subtypes.

This should allow us to make an examination of as many patients diagnosed with the disease as possible, leading to an understanding of the complexity of the disease, its various subtypes, and the response to standard and then experimental treatments. Analysis of the brain biopsy tissue will allow us to investigate this further and to forecast improved treatments, and in the end to allow us and others to diagnose the condition with certainty, at an earlier stage, and to instigate a more powerful and successful treatment, which in the end should help prevent the condition from damaging the brain, leading to a greater chance of a much more satisfactory outcome.

Table 1: causes of secondary angiitis of the central nervous system

| Infections: | viral: EBV, CMV, VZV, HIV, parvovirus B19, west Nile virus, hepatitis C |
| | bacterial: TB, mycoplasma, Str pneumoniae, T pallidum, B burgdorferi |
| | Fungal: candida, aspergillus, actinomyces, mucormycosis |
| Radiotherapy |
| Connective tissue diseases: SLE, Sjogren’s syndrome, rheumatoid arthritis, sarcoidosis |
| Systemic vasculitis: Takayasu’s arteritis, polyarteritis nodosa, GPA*, EGPA*, cryoglobulinaemia |
| *Granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis |

Table 2: Diagnostic criteria for PACNS (Calabresi LS, Mallek JA. Medicine (Baltimore)1988; 67: 20 – 39)

| The presence of an acquired otherwise unexplained neurological or psychiatric deficit |
| The presence of either classic angiographic or histopathological features of angiitis within the CNS |
| No evidence of systemic vasculitis or any disorder that could cause or mimic the angiographic or pathological features of the disease |