GIANT CELL ARTERITIS DEMENTIA AND OTHER STEROID-RESPONSIVE DEMENTIA SYNDROMES ARE A UNIQUE OPPORTUNITY FOR CLINICIANS AND RESEARCHERS

Dear Sir,

When evaluating patients with dementia, it is common to check for easily reversible problems, such as hypothyroidism, normal pressure hydrocephalus and B12 deficiency. Although these are not usually the main cause of a patient's troubles, correcting them improves chances for preserving, or at least stabilising, cognitive status. This letter makes the argument that both clinicians and researchers should give more attention to looking for giant cell arteritis (GCA) and other steroid-responsive conditions, as a routine part of the standard dementia workup.

GCA is the most common cerebral vasculitis among the elderly of European ancestry, with an incidence on the order of 1–10 per 100,000.[1] The prevalence of GCA in other ethnic populations is not well known, but in one survey in Japan, prevalence was estimated at one per 100,000.[2] It was once believed that GCA did not exist in China or India, but verified cases have been documented over the past two decades; a recent report suggests that the incidence of GCA in China might be significantly underestimated.[3,4] Similarly, it is thought that among African-Americans in the United States, there might be many occult, unrecognised cases of GCA.[5] The typical GCA presentation is an elderly patient with headaches or visual loss, an elevated sedimentation rate, associated symptoms of proximal muscle stiffness (polymyalgia rheumatica), anaemia and a temporal artery biopsy showing giant cell arteritis.[1] GCA is treated with high dose corticosteroids (prednisone 60 mg per day, prednisolone or intravenous solu-medrol at comparable potencies). Steroids are continued for many months with a very gradual tapering.[1]

Proof-of-principle that dementia caused by occult, unrecognised GCA, that otherwise might be written off as typical Alzheimer's disease or vascular dementia, can be established from published case histories. For example, in 2005, a 76-year-old man presented with acute right-sided periocular pain and diminished vision. He had a sedimentation rate of 73 mm/hr, cilioretinal artery occlusion and "florid" GCA seen on temporal artery biopsy. He was quite impaired cognitively, but prednisolone 50 mg per day produced rapid normalisation of his mental status, and at that point, his family commented that he had actually had dementia for at least a few years. Further investigation revealed that three years before, he had suffered a right-sided middle cerebral artery stroke that had been accompanied by scalp tenderness and right-sided headache. A diagnosis of GCA had been considered at that time but was not pursued because sedimentation rate was only 4 mm/hr.[6]

There are other steroid-responsive conditions that are even rarer than GCA, that can also manifest with dementia. In 1999, a report was published describing five patients, aged 54–80 years with chronic dementia of weeks to months duration, that proved on brain biopsy to be a newly-defined syndrome termed, "nonvasculitic autoimmune meningoencephalitis", characterised by inflammation in the meninges and brain tissue but not the blood vessels.[7] The underlying autoimmunity in the five patients was variable, with one patient having no detectable autoantibodies, while the others had a mixture of different autoantibodies, including antinuclear antibody, rheumatoid factor, anti-Sjogren antibodies and antithyroid anti-microsomal antibodies. Following high-dose steroid administration comparable to that used for GCA, the patients showed substantial or complete recovery of cognitive function over a matter of days to weeks.[7] Similar rapid dramatic turnaround after high dose steroids in patients with subacute or chronic cognitive decline has also been seen with Hashimoto's encephalopathy, granulomatous angiitis of the central nervous system, idiopathic hypereosinophilic syndrome and spontaneous intracranial hypotension.[8-11] Diagnosis was made by brain biopsy or characteristic brain imaging findings supported by laboratory studies.

A systematic research programme should be undertaken to improve identification of patients with steroid-reversible dementia syndromes. Routinely checking sedimentation rate could be a useful screening tool for GCA dementia, but one must not overlook the possibility of GCA, or these other disorders, presenting with a normal sedimentation rate.[12] Typically, since GCA involves large cranial arteries, one should look for patients with localising neurological signs from completed cerebrovascular accidents, as the 76-year-old man cited above illustrates.[6] In a series of similar cases from a 1990 report, GCA presented with large vessel strokes, and successful initiation of steroids prevented further damage, while leaving unchanged the results of the completed strokes.[13] However, GCA dementia can also resemble insidious Alzheimer's disease or small vessel multi-infarct dementia, with a gradual worsening of symptoms, an absence of focal neurological deficits and apparent complete-reversal from steroids.[14,15] Given this unpredictability, not to mention the wide range of presentations for other steroid-reversible conditions, it is clear that new techniques and guidelines for identifying steroid-responsive conditions need to be promoted, using noninvasive screening short of temporal artery and brain biopsies. Positron emission tomography (PET) scanning offers one possibility, as illustrated by another published case with excellent brain images, that could serve as a model for future programmes. An 81-year-old woman

with biopsy-proven GCA had dementia that was partially reversed with steroids, and nuclear medicine scanning showed improved cerebral circulation after this steroid treatment. Prior to administration of high-dose steroids, her cerebral perfusion scan looked like someone with Alzheimer's disease, with a noted decrease in parietal regions bilaterally. After one year of treatment, there was a persistent perfusion deficit on the left side, but perfusion to the right parietal lobe was almost normalised.[16] Alongside PET scanning, temporal artery ultrasonography and genetic polymorphisms are currently under investigation for identification of GCA.[17,18] These could be used to screen for GCA in patients with dementia, and identification of genetic polymorphisms might facilitate diagnosis of the other conditions as well.

A serious effort to find GCA dementia and other steroid-reversible dementia syndromes would require the collaboration of primary care physicians and neurologists to do clinical evaluations, radiologists to interpret imaging, surgeons or ophthalmologists to do temporal artery biopsies, and pathologists to read the biopsies. Furthermore, a very large referral base would be necessary. In one Swedish study, a postmortem series of 1,097 randomly-selected elderly subjects found 12 cases of GCA, of which had not been diagnosed prior to death, corresponding to about 1% of those patients having undiagnosed GCA.[19] If 1% of total dementia cases were caused by occult steroid-reversible conditions, several hundred patients would have to be screened to find just a few for study. Inevitably this would require a large multicentre study, to have the necessary specialists and patients, ideally an enterprise with researchers from many different parts of the world. The need for a large referral base would be even more true for the other steroid-reversible dementia syndromes, because of their rarity, and a collaborative international effort would be the only way to proceed. In the meantime, practising physicians around the world can do their part, by being vigilant for steroid-reversible conditions when working up patients with dementia and publishing any new cases.

Better identification of steroid-reversible syndromes, a routine part of dementia care, could have a dramatic impact, even if the number of patients identified is relatively small and their improvement is sometimes only partial. At the very least, it would advance the concept that we can change the natural history of dementia, and this would carry over to the larger fight against Alzheimer's disease and conventional multi-infarct dementia. Furthermore, every individual patient with a steroid-reversible condition recognised, thanks to increased attention, would in itself justify our collective efforts. Thus, this idea is put forward now in the *Singapore Medical Journal* in the hopes of being the catalyst for many new victories, both small and large.

Yours sincerely,

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