Current Concepts in Optic Neuritis

The Optic Neuritis Treatment Trial (ONTT) has been the largest study on optic neuritis to date, revealing the presentation, course and prognosis of optic neuritis and has heavily influenced the treatment protocol for acute isolated optic neuritis around the Western world. The results of the final follow-up from this study have recently been published and reiterate the prognostic role of magnetic resonance imaging in optic neuritis.

The ONTT trial was conducted, however, in an era preceding the discovery of the aquaporin 4 autoantibody, which has been recognised as a biomarker for neuromyelitis optica (NMO).

Aquaporin 4 autoantibody

The discovery of the Aquaporin 4 autoantibody was reported in 2004. Immediately prior to its discovery, NMO was starting to be recognised as both a monophasic and a relapsing and remitting illness (Figure). However, at the time of the conduction of the ONTT, NMO was not included within the differential diagnosis of cases of ‘typically presenting’ acute isolated optic neuritis. Although approximately 3% of patients enrolled in the ONTT had a visual acuity of 6/60 or worse, five years following an episode of optic neuritis, none of these patients were considered to be suffering from an NMO-related disorder at the time.

Shortly after the aquaporin 4 autoantibody was discovered, various reports describing neurological presentations outside of the hallmark syndrome of optic neuritis and transverse myelitis were increasingly described, in conjunction with the presence of the aquaporin 4 autoantibody. This led to the birth of a new concept of ‘NMO spectrum’ disorder.

The advent of the concept of an NMO spectrum disorder has challenged existing protocols in the treatment of acute isolated optic neuritis. The occurrence of an isolated acute optic neuritis in the absence of any other underlying sign of disease on clinical examination, serological testing and imaging can no longer be classified as a ‘clinically isolated syndrome’ (CIS) without first testing for the aquaporin 4 autoantibody. In the presence of antibody positivity, acute isolated optic neuritis becomes an NMO spectrum disorder and as such the ONTT derived protocol (involving either a short course of intravenous corticosteroids or a ‘conservative management’ protocol for its management becomes less appropriate.

Although there has been no randomised controlled study on the acute treatment of NMO-related optic neuritis, a recent study reports that the administration of intravenous corticosteroid therapy within 48 hours of the onset of optic neuritis may prevent irreversible retinal nerve fibre layer loss.

The presence of aquaporin 4 autoantibodies also influences the long-term management of a patient following optic neuritis. Prolonged immunosuppression has been shown to reduce the relapse rate in NMO and may be initiated after its first presenting symptom.

Following the identification of the NMO spectrum disorder, there is now a wider clinical appreciation of the possibility of a patient presenting with acute isolated optic neuritis having NMO. The incidence of aquaporin 4 autoantibody positivity in Western Europe has been recently shown to be higher than previously believed. As a result, there is renewed interest in the identification of NMO spectrum disorder, even before seroanalysis for the aquaporin 4 autoantibody has been undertaken.

Other biomarkers and optic neuritis

Attempts to identify NMO spectrum disorder as the underlying aetiology of optic neuritis through serological analysis for biomarkers have met with some success. Recent reports suggest that serum levels of glial fibrillary acidic protein (GFAP), a marker of astrocytic damage, as well as N-acetyl aspartate may be elevated in NMO spectrum disease, compared with MS, and may help to distinguish between the two. Serum GFAP levels have also been shown to be elevated despite the absence of extra-optic nerve disease. Such tests may be incorporated into the standard workup for optic neuritis in the future.

Ethnicity and optic neuritis

Approximately 15% of patients enrolled in the ONTT were of African-American ethnic origin (59 out of 448 patients), although a separate analysis with respect to ethnic background was

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not carried out for the majority of the trial. Traditionally, the ethnic background of a patient has not been separately considered when managing a case of acute isolated optic neuritis. A recent study however, has suggested there may be a differing genetic susceptibility to NMO and MS. More recently, a report from the United Kingdom on the incidence of optic neuritis within an ethnically diverse patient population has suggested there may be an ethnicity bias on the incidence of optic neuritis within an NMO patient cohort. Despite only 14% of all patients presenting with acute isolated optic neuritis with no previously known underlying cause (who did not develop a collagen-vascular/ granulomatous/ infectious/ autoimmune/ neoplastic illness to account for the optic neuritis over the course of 16 months) being of African or African-Caribbean descent, 63% of all patients presenting with NMO-related optic neuritis over three years were of African or African-Caribbean descent. These findings suggest that a patient’s genotype and phenotype should be taken into consideration when forming a management plan in the acute setting of optic neuritis.

The future

An episode of acute isolated optic neuritis is viewed differently today from how it was viewed twenty years ago, when the ONTT was first conducted. Traditional markers of visual function showed an optimistic picture of visual prognosis following optic neuritis and contributed to ONTT based management protocols in which intravenous corticosteroid therapy and conservative management were deemed to be of equal efficacy. The concept of an NMO spectrum disorder was unknown and NMO did not score highly on the differential diagnosis of optic neuritis. Little consideration was given to genetic factors and to the patient’s ethnic background.

The discovery of the aquaporin 4 autoantibody has profoundly improved diagnostic and prognostic accuracy. It has encouraged a strong deviation away from ONTT based protocols in some cases of optic neuritis where NMO spectrum disease may be the underlying aetiology. Additional factors are now recognised which need to be considered before deciding on the management of an acute episode of optic neuritis. The ONTT must now be revisited in the aquaporin 4 autoantibody era in light of recent findings. A further large scale study is also indicated to consider how serological markers such as GFAP and N-acetyl aspartate and genetic influences can influence the management and outcome of acute isolated optic neuritis.

REFERENCES