Anti-NMDA Receptor Encephalitis

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Abstract

In recent years, the discovery of antibodies to specific neuronal antigens that then go on to cause encephalitis has gone a long way to change the investigation and management of a potential encephalitic process. These have now become known under the umbrella term of the ‘autoimmune encephalitides’. In this article we look at anti-N-methyl-D-aspartate receptor encephalitis, a condition most often found in young females and has an association with a number of malignancies, most commonly ovarian teratomas. Most patients will have a viral prodrome, followed by psychiatric, seizure, dysautonomic and dyskinetic features, but can present at any point along this pathway. Treatment involves prompt tumour identification and removal where appropriate and initiation of immunosuppressive therapy, usually commencing with corticosteroids. A substantial proportion of patients will make a full recovery, but many will need medical, psychiatric and social care following completion of the acute phase of the illness.

Keywords: Autoimmune; Encephalitis; NMDA receptor antibodies

Introduction

In the last few years there has been the identification of a number of new neuronal antibody targets that are now proven to be the underlying cause of what are now under the umbrella term of the autoimmune encephalitides. In this article we look at one of these disorders; anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, aiming to cover the epidemiology, pathophysiology, clinical features, investigation and treatment.

Epidemiology

With increasing physician awareness more and more information regarding the epidemiology of anti-NMDAR encephalitis is known and thus the exact incidence cannot yet be fully determined. The largest series of over 400 patients found that at least 80% of sufferers are female [1], with the preceding paper finding 20% of sufferers under the age of 19 [2], and a smaller series finding the mean age of presentation at 18.5 years [3]. Despite this we found a case age range spanning from 20 months [4] to 84 years old [5], implying that this is a condition to be considered in all age groups where a diagnosis of encephalitis is considered. This mean age may drop down further, particularly with the increasing identification of paediatric cases which can present with more atypical features. Anti-NMDAR encephalitis has been reported to have a predilection in Asian and Pacific Islanders [3] (possibly representing geographical variances affecting selected patients) and the finding of associated ovarian teratoma is more common in Black females [2].

Like its limbic encephalitis counterpart, anti-NMDAR encephalitis has associations with a number of malignancies. The commonest association is with ovarian teratomas, one series reporting the presence at 59%. [2]. Tumour diagnosis is almost always made following onset of the neurological syndrome, but independent diagnosis of the tumour outside of this context should remind the treating clinician to look out for and inform the patient of the features of anti-NMDAR encephalitis such that its recognition and treatment are both swift. Florance et al. focused upon a case series to compare the incidence and pathology of anti-NMDAR encephalitis in children and adults [6]. The study included 81 patients in total. Of the female patients 56% of those greater than 18 years of age and 31% of those under 18 years of age were found to have an ovarian teratoma. Patients under the age of 14 years were less likely to have underlying malignancy with only 1 detected out of 11 patients with anti-NMDAR encephalitis [6]. This is analogous to the theory that the younger the patient the reduced likelihood of an identifiable tumour [7]. Of this case series 12 (14.8%) male patients were recognized and in this instance no underlying tumour was associated. In a previous case series though, 2 out of 9 males were identified as having associated malignancies which included bilateral testicular seminoma and teratoma [6,8] and small cell lung cancer [2].

Other known tumour associations include mediastinal teratomas and sex-cord stromal tumours [1] and there have been reported links with neuroblastomas [9] and Hodgkin’s lymphoma [10]. We also found a report of a possible link with the Tdap-IPV vaccine (for tetanus, diphtheria, pertussis and polio), with the patient having a prodromal illness 24 hours post vaccine and classical psychiatric symptoms 5 weeks later [11].

Pathophysiology

The association between limbic encephalitis and malignancy is well established with the antibodies targeting intracellular neuronal structures. The anti NMDA receptor is an extracellular target and as such the receptor to function, both subunits must be bound to their substrate NR1 which binds glycine and NR2 which binds glutamate. For the receptor to function, both subunits must be bound to their substrate NR1 which binds glycine and NR2 which binds glutamate. For the anti-NMDA receptor to function, both subunits must be bound to their substrate NR1 which binds glycine and NR2 which binds glutamate. For the anti-NMDA receptor to function, both subunits must be bound to their substrate NR1 which binds glycine and NR2 which binds glutamate. For the anti-NMDA receptor to function, both subunits must be bound to their substrate NR1 which binds glycine and NR2 which binds glutamate.

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leads to depression of its activity. It is hypothesised that hypo-activity of the receptor plays a role in the pathogenesis of schizophrenia and hyperactivity linked to conditions such as dementia and some forms of epilepsy [2]. In anti-NMDA receptor encephalitis, antibodies are against the NRI subunit of the receptor.

Hughes et al. [12] cultured hippocampal neurones in cerebrospinal fluid (CSF) containing anti NRI receptor antibodies. This led to a decrease in the number and density of NMDA receptor clusters. The test was then repeated with CSF of patients at later stages of the disease and this again showed a decrease in receptor density, but not as marked as the initial disease onset, thus showing a causal relationship between NMDAR antibody levels and disease activity. Neuronal signals relying on anti-NMDA receptors were reduced by anti-NR1 receptor antibodies showing that the effects of the antibodies were reversible. Importantly, no structural damage to the neurones was observed [12]. However, when we look at neurohistochemical findings from sufferers, Tuzun et al. found temporal lobe and hippocampal atrophy, loss of pyramidal neurones in the hippocampus and quite extensive gliosis in the hippocampus, basal forebrain, basal ganglia and spinal cord, consistent with areas of known receptor concentration. Unlike other forms of limbic encephalitis, there was no lymphocytic infiltration [13]. These findings are interesting, given that in the laboratory no structural damage was observed to the neurones, but the presence of gliosis would imply that there must be an inflammatory aspect at some point during this process leading to scarring and thus may well explain the prolonged or incomplete recovery that many patients go on to have.

Antibody production to the NMDA receptors are produced to a much greater degree in cerebrospinal fluid, with levels in active disease up to 10 times higher in the CSF compared with serum and high levels of antibody secreting cells in the CSF [14]. Low levels of complement in the CSF implies this pathway is not involved in the disease [15] and a lack of disruption in the blood brain barrier in pathologically examined specimens [14] means it is not completely clear what the mechanism is that starts the autoimmune process.

Clinical Presentation

For 60-86% of patients the illness will begin with what are often benign symptoms and thus are usually only considered as the start of the illness in hindsight [2,3]. These include headache, low-grade fever, fatigue or irritability. Symptoms typically last up to five days [16], but can occur two or more weeks before other features of the illness.

Psychiatric symptoms occur next in 68-77% of patients [2,3] and may be the first contact the patient has with medical services, often under the care of a psychiatrist. Nearly all patients have personality change and 68% develop symptoms of psychosis such as hallucinations (particularly auditory), compulsive ideation and delusional thought processes [3]. Cognitive decline also occurs during this stage, with patients’ exhibiting flat, disorganised thinking and poor language skills including a reduction in verbal output, echolalia and mutism [1,16,17].

Up to 76% of patients will develop seizures [2]. This may be part of the presenting symptoms, but generally occurred post admission in 60% of individuals [3]. In one study, the majority (46/76 in 2008 study) [2] suffered generalised tonic clonic seizures and a minority (10/76) experienced complex partial seizures. The remaining patients’ seizures were not specified. Cases of complex partial status epilepticus [17], refractory status epilepticus [18] and even ictal asystole [19] have been reported to occur in anti-NMDA encephalitis.

A deterioration in psychiatric systems will often herald the onset of a catatonic state, followed by reduction in conscious level (up to 88% of patients will have this) [2]. In his 2008 case series, Dalmat reports a 66% incidence of central hypoventilation requiring intensive care admission and intubation [2]. A dissociative response to stimuli (e.g. resisting eye opening but showing little or no response to painful stimuli) has also been reported [16].

Dyskinesias are described in up to 86% of patients [2]. These abnormal movements may take the form of choreoathetoid movements, ataxias, cranial nerve palsies or oro-facial dyskinesias, lip-smacking, chewing or dystonic posturing of the fingers [16]. The latter is particularly important as alternative routes of feeding may need to be sort. The movements are independent of any form of seizure activity and do not correlate with electroencephalographic (EEG) abnormalities [20].

Dysautonomia is reported with a frequency of 69-89% [2,3] in varying studies. This includes hyper/hypothermia, tachycardia, bradycardia, hypersalivation, hypertension, hyponatremia, urinary retention and erectile dysfunction [2,21]. Some dysautonomic manifestations are so severe they necessitate intensive care management. Gable et al. reported most patients in their small cohort had at least 3 dysautonomic features. In one series 37% of patients had a cardiac dysrhythmia, with 4 patients requiring pacemaker insertion [3]. In a classic presentation of anti-NMDAR encephalitis, many patients will progress through the phases listed here, but they can present at any point and so the diagnosis must be considered in a patient presenting with any of these features together with taking a careful history of clinical features prior to presentation.

Clinical features in those under 18 years of age were found to differ. In 48% of cases children had a prodrome of fever, headache, upper respiratory tract symptoms or diarrhoea and vomiting. Almost all patients presented to the physician with mood or behavioural changes such as temper tantrums [22], hyperactivity or irritability as opposed to frank psychosis making the diagnosis of an underlying pathological cause less obvious [1]. In addition it is thought that movement disorders and seizures; usually partial motor or complex seizures; occur earlier in the disease process, however, it may be that this is just the first recognisable symptom [1,6].

Autonomic instability (tachycardia, hyperthermia and hypertension) occurred in 86% of those under 18 years of age and although many were affected it appeared to be less severe than in adults. In children mechanical ventilation was required by 23% for central hypoventilation and 19% for airway protection. Transient oxygen desaturation which did not require ventilator support occurred in 16% of patients [6].

Investigations and Diagnosis

Investigations should aim to confirm the diagnosis while excluding mimics. Where an encephalitic illness is suspected serum and CSF assessment for anti-NMDA receptor antibodies should be undertaken alongside viral serology and limbic encephalitis screening to establish a laboratory diagnosis [5]. CSF antibody levels can be up to 10 fold that of serum [14] and in the largest case series to date, there was not a case of anti-NMDA receptor encephalitis where CSF antibodies were not present [1] and thus a lumbar puncture should always be performed. Where serum antibodies are found, they can provide a useful marker for monitoring disease activity as reduction in these levels has a good
correlation with clinical outcome, but a negative initial serum antibody does not rule out the diagnosis. Antibody titres are highest in those with an associated malignancy and those with severe symptomatology [2].

Around 90% of patients with anti-NMDAR encephalitis demonstrate a lymphocytic pleocytosis during the course of the illness [2,3,24]. Other findings include an elevated CSF protein and in 60% of patients CSF-specific oligoclonal bands occur. Glucose count is often within normal limits. In early disease EEG monitoring may show evidence of seizure activity during and between seizure episodes, but by far the most common abnormality is that of diffuse non-specific slowing [3,24,25], which will usually normalise once effective treatment is commenced. Non-convulsive status epilepticus is reported, but is by no means a hallmark of the disease [1,3].

Imaging has a very limited role in helping to formulate a diagnosis of anti-NMDAR encephalitis, with little or no pathognomonic features. Computed tomography provides no additional information. Gable et al. report normal magnetic resonance imaging on admission, with subsequent changes in 40% of patients [3]. Magnetic resonance imaging (MRI) changes are of limited consistency and will range from periventricular white matter changes similar to demyelination to hyperintensities in the white matter of the hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, pons and, in rare occasions, the spinal cord on fluid-attenuated inversion recovery/T2 sequences [12,18,24,26]. These changes are seen in up to 55% of patients.

Single-photon emission computed tomography studies showed no significant focal changes in the acute phase of illness in 75% (3 patients); however, in one patient frontotemporal hyperperfusion was noted in the early stage and hypoperfusion during the period of recovery was noted in two patients [16]. Fluorine-18 Fluorodeoxyglucose Positron emission tomography–computed tomography (18F FDG PET/CT) imaging can be performed under EEG monitoring in those patients presenting with features of anti-NMDAR encephalitis in order to confirm or rule out the presence of teratoma or any other possible sites of malignancy [27]. It is also a non-invasive way in which to provide information on the functioning of the brain at a biochemical and metabolic level [28].

In general it is thought that brain PET is more sensitive than MRI, however findings can be variable depending on which phase of illness is ongoing at the time of the scan. In the acute phase FDG-PET generally shows cerebral hypermetabolism anteriorly, with relative diffuse posterior hypometabolism. For example in the case published by Chanson et al. [29] two foci of increased marker fixation were identified including left prefrontal cortex and anterior cingulate cortex, the increased uptake in these areas were thought to correlate with clinical findings of abnormal movements of the right foot and psychiatric symptoms respectively [29,30]. These findings are not exclusive with focal cerebellar hypermetabolism and diffuse hypometabolism elsewhere has been reported as a novel finding in a paediatric case [31]. Literature proposes that further FDG-PET scanning in cases of anti-NMDAR encephalitis is warranted in order to categorise those areas of the brain most affected [28]. PET findings in relapsing cases have demonstrated reduced FDG uptake in the cerebral cortex indicating reduced metabolic rates whereas in follow up patients who have made a good recovery FDG-PET findings were normal. This supports the theory that brain injury sustained during anti-NMDAR encephalitis is reversible [28,32].

Malignancy Screening

Anti-NMDAR encephalitis usually precedes the discovery of an associated malignancy which poses a question regarding appropriate screening for follow up patients. Potential screening imaging modalities include ultrasonography or CT abdomen/pelvis. Each investigation poses its own set of problems. For example in very young females a trans-vaginal ultrasound may be too invasive but the alternative of surveillance computed tomography scans would lead to high levels of radiation exposure. Florance et al. recommended periodic ultrasonography and MRI of the abdomen and pelvis for at least two years following diagnosis, although there is no good data or guidelines to that effect. Tumour surveillance for males was not recommended as the number of cases has been too small [6]; although initial imaging to rule out testicular and thoracic malignancies would not seem unreasonable as prognosis is better in those patients with associated malignancies. We would recommend that every individual should undergo at least initial malignancy screening, especially as treatment of this offers a better prognosis. We do not know whether anti-NMDAR encephalitis may pre-date malignancy as in conditions such as dermatomyositis. If evidence for this were to emerge then it may well make the basis for more long term screening much more justifiable.

Iizuka et al. reported four cases of young Japanese women (17-33 years) who had previously been diagnosed with ‘Juvenile Acute Nonherpetic Encephalitis’ between 2000-2003. In 2007 archived serum and CSF fluids from the time of symptom onset for all four patients revealed antibodies to NR1/NR2B heteromers of the NMDAR, thus supporting a diagnosis of anti-NMDAR encephalitis. This finding prompted a recall of patients for serum antibody titres, and tumour screening (MRI scan pelvis). Serum antibodies were no longer detectable but MRI revealed a cystic mass supportive of a diagnosis of an ovarian teratoma in three patients. In retrospect one patient had had an incidental finding of an ‘ovarian cyst’ at the time of the acute illness but the significance had not been realised. All three patients underwent surgical removal and histology confirmed the diagnosis of mature cystic teratoma with neural tissue [16].

From this it is speculated that in those cases where a tumour is identified, recovery may be hastened by prompt tumour resection. Uchino et al. reported a case where early recognition and surgical resection of a teratoma, in the context of anti-NMDA receptor encephalitis, led to clinical signs of recovery within 2 weeks of the operation [33]. This patient had a total hospital stay of 11 weeks as opposed to those patients in the case report by Iizuka et al. who did not undergo surgery due to lack of formal diagnosis and had hospital admissions ranging from 2 to 14 months [16]. In addition, the patient reported by Uchino et al. also received intravenous Methylprednisolone (IVMP), intravenous immunoglobulin (IVIG) and plasma exchange; despite these interventions it is still thought that the concept of prompt tumour removal expedited recovery significantly [33]. It is also important to note that anti-NMDAR encephalitis may precede the onset of ovarian teratoma by years and that although recovery may occur without tumour removal the severity and extended duration of symptoms supports tumour removal [16].

Treatment

Treatment of anti-NMDA receptor encephalitis involves dealing with the acute effects of the disease, removal of any underlying causative tumour, induction of immunosuppressive therapy and management.
of long term residual deficits following remission of the autoimmune process. The treating physician must remember that features of the disease cross the borders of many medical specialties and thus management must always be that of a multi-disciplinary approach.

Features of psychosis should initially be managed in the conventional way, with antipsychotic therapy of the physicians’ choice or local protocol. Some series have reported a significant reduction or resolution in psychiatric symptoms with electroconvulsive therapy [20,22,34,35] although the physiological basis for this has not been defined. Reduction of such symptoms may well lead to unmasking of other features of the disease, which can then be appropriately treated.

Seizures in the context of anti-NMDAR encephalitis are often difficult to manage and can require multiple agents or an infusion of benzodiazepine [36]. A 2009 case report details prolonged non convulsive status epilepticus refractory to phenytoin, levetiracetam and valproic acid and incompletely suppressed by benzodiazepines. Phenobarbitol induced coma did manage to control seizure activity but over a five month period each attempt to withdraw the medication resulted in resumption of status epilepticus. Treatment with IVIG, rituximab and cyclophosphamide had no benefit on clinical state. Multiple ultrasound scans of the ovaries revealed a haemorrhagic cyst which was considered an incidental finding. After 5 months of phenobarbitol induced suppression the patient underwent an oophorectomy with histology confirming an ovarian teratoma. At this stage it was possible to wean phenobarbitol over the course of 5 weeks without seizure activity recurring [23].

When anti-NMDAR encephalitis is found to be paraneoplastic, early tumour resection along with immunotherapy is the recommended best practice and this leads to better outcomes and reduction in symptomatology. The most reliably documented experience is with ovarian teratomas [33]. An interesting ethical scenario will begin to develop around this issue. There have been at least two reports of patients with confirmed anti-NMDA receptor encephalitis who have had no radiologically identifiable ovarian mass; have not responded to immunosuppressive regimes and have then gone on to have empirical oophorectomies with identification of teratomas on post-operative histological examination [23,37]. This is of particular interest in the younger cohort of patients who are currently believed to be less likely to have such malignancies, based on a lack of radiological findings. Not surprisingly, we did not find any reports of the practice whereby an oophorectomy was performed and histology negative, but this certainly raises an ethical issue of how far we should go to find the presence of an underlying tumour; particularly when conventional treatment has failed.

In patients where no underlying tumour is identified, first line immunotherapy will often be intravenous methylprednisolone. Alternative initial approaches include intravenous immunoglobulins or plasma exchange [2]. However, plasma exchange can be difficult to perform in children and uncooperative patients or if there is autonomic instability [1]. In fact one very small case series reported a complication rate with plasma exchange of 20% [38]. In relation to the use of therapeutic plasma exchange (TPE) as first line treatment, The American Society for Apheresis has actually assigned it as a category III (grade 2C) recommendation. This means that it should only be considered as a second line therapy either in conjunction with or after failure of first line treatment such as corticosteroids. Despite this many case reports have attributed clinical improvement to the commencement of plasma exchange and so revaluation of guidelines may be required as more experience is gained [39,40].

Second line immunotherapy includes rituximab, cyclophosphamide or azathioprine; unfortunately as yet there is no literature available to compare treatments, but a multitude of case reports exist to support each individual approach. Indications for second line immunotherapy include if there has been a delayed diagnosis or if there has been no response to first line therapy after 10 days. Paediatric physicians will often use a single agent for second line immunotherapy which is usually rituximab. The treatment regime is continued until a substantial clinical improvement has been made and this normally correlates with reduced concentration of antibody in serum and CSF. In the majority of cases anti-epileptics can also be stopped at this point. Immunosuppression can be continued for at least one year with a steroid sparing agent after initial immunotherapy is discontinued to prevent clinical relapse [1,4,25,41].

Other treatment response observations include a report from a Children’s Hospital where 8 patients were diagnosed and received treatment for anti-NMDAR encephalitis. The physicians found that although some children responded rapidly to IVIG or IVMP others had less marked responses. Individual patient response may also be variable between treatment sessions and some children made a slow improvement seemingly independent of treatments used. The overall consensus was that immunotherapy had variable effects on clinical course and that those patients who presented with an associated tumour were more likely to make a full recovery than those without a tumour [6].

Prognosis

Mortality stands at 4% [1] (with an average time to death 3.5 months after presentation) in more comprehensive series to 10% in smaller ones [3]. Prognosis is far better in individuals with an identifiable associated malignancy; providing it is found and treated within 3-4 months from symptom onset. When anti-NMDAR encephalitis is associated with an underlying tumour the outcome can range from spontaneous recovery despite the tumour not being resected to severe residual deficits or death with a mortality rate of 7% [2]. Causes of mortality include sepsis, sudden cardiac arrest, acute respiratory distress, refractory status epilepticus and tumour progression [1].

Non- neoplastic patients generally have a poorer prognosis. None the less, in classical disease recovery is slow and many patients can spend the first few months of their disease as a hospital inpatient. From Dalmau’s 2008 series of 100 patients: 47 made a complete recovery, 28 had mild stable deficits, 18 had severe deficits and 7 died [2]. However, 85% of patients had some degree of frontal lobe dysfunction, a functional discrepancy echoed by Finke et al. who found that in their small cohort of patients, significant deficits in frontal lobe function was found in 8 out of 9 individuals, deficits of a smaller degree being associated with adequately treated disease [42].

Relapsing disease will affect 20-25% of patients with anti-NMDA encephalitis [1]. Defining relapse as any new neurological or psychiatric syndrome that improved with immunotherapy, Gabilono et al. observed 13 relapses in 6 patients with average time to relapse of 2 years (range 0.5-13 yrs), giving a median of 0.52 relapses per patient per year [43]. Dalmau et al. in their much larger series, observed a similar relapse percentage, with an average onset of 18 months [1]. Relapses were less common in patients who had a concomitant tumour
found and treated and were more likely to occur in patients who didn’t receive immunotherapy, which further emphasises the importance of rapid screening and treatment for known associated malignancies and initiation of concomitant immunotherapy.

Izuza et al. have demonstrated reversibility of structural brain anomalies in two patients. Atrophy seen in the medial temporal and frontotemporal lobes respectively some months after diagnosis was markedly improved at repeat scanning 7 years later. SPECT studies initially showed marked hypoperfusion in these areas, with significant improvement on follow up scanning. These cases show that in anti-NMDAR encephalitis brain atrophy in conjunction with severe and protracted symptoms does not directly correlate with a poor clinical outcome. It would appear that the brain has an ability to recover from brain atrophy associated with anti-NMDAR encephalitis and that in part the disease is at least a functional, rather than a structural one, however, the exact mechanism for reversible brain atrophy is not yet known [32].

Prognosis in children was studied by Florance et al. who followed up 31 patients diagnosed with anti-NMDAR encephalitis under the age of 18 years for 4.5 months. Of these patients 29% (9 patients) had a full recovery; 45% (14 patients) substantial improvement, living at home, with mild deficits and 26% (8 patients) had made limited improvement. However, all patients continued to show signs of slow recovery. In this study those who are said to have made limited improvement are either living at home, in a rehabilitation centre or in hospital with minimal change in neurological status 3 months after presentation [6]. This study has a very short follow up period though and so it would be prudent to present data where patients presenting in childhood had been followed for a longer time course. In the same study 25% had either one singular episode or several similar episodes of suspected anti-NMDAR encephalitis prior to formal diagnosis (thereby suffering relapsing encephalitis). Four patients had relapsed upon tapering of corticosteroids or cessation of immunotherapy and another four relapsing encephalitis). Four patients had relapsed upon tapering of corticosteroids or cessation of immunotherapy and another four patients relapsed more than 1 year after full recovery. This leads to the clinical dilemma as to whether long term immunosuppression would be beneficial [6]. It is worth noting however that in two paediatric case reports where cyclophosphamide was used as the secondary treatment long term immunosuppression was not given and none of the three patients relapsed at 2 year follow up [44].

Regardless of treatment regime all patients are highly likely to require several months of physical and behavioural rehabilitation following the acute phase of illness, in order to help deal with the functional deficits provided by the varying degrees of frontal lobe dysfunction and possible memory and language deficits that may still exist following recovery of the acute phase of the illness. This is especially important in younger patients for whom such deficits may well require a lifetime of medical and remedial support.

In conclusion, anti-NMDAR encephalitis is an emerging disorder quite possibly underpinning many of the so labelled encephalitis of unknown origin. Although the classic spectrum is that of a viral prodrome, psychiatric, seizures, autonomic and dyskinetic features, the clinician should be aware that presentation of the disease may be in any of these stages. Lumbar puncture and CSF assessment for examination is a mandatory requirement for diagnosis and we would advise at least initial screening for known associated malignancies, especially in young females. Corticosteroids appear to be heralding their place as first line treatment, but once consideration of the diagnosis becomes uniform in clinical practice, we need good randomised control trials to guide us further in future management strategies.

Conflict of Interest
The authors declare no conflict of interest

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