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Movement disorders in multiple sclerosis and their treatment

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Hyperkinetic movement disorders such as tremors are not uncommon in patients with multiple sclerosis (MS). The classical feature is intention tremor, whereas rest tremors appear not to occur. Treatment is mainly invasive, with options of Gamma Knife surgery, thalamotomy or deep brain stimulation depending on individual circumstances. Deep brain stimulation is the only option for patients who require a bilateral intervention. All treatment recommendations have only low evidence. Tremors can also be cured spontaneously by a subsequent strategic MS lesion. Paroxysmal dyskinesias are rarer than tremors. The rarest MS movement disorder is symptomatic paroxysmal choreoathetosis, tonic spasms or 'brain stem fits'; attacks are short but frequent, up to 200 per day and generally respond well to carbamazepine.

Tremor in multiple sclerosis

• Epidemiology & clinical features

Hyperkinetic movement disorders such as tremors are not uncommon in patients with multiple sclerosis (MS). Until quite recently, published information about tremor in MS had been limited to two smaller studies [1,2]. In 2015, the most recent analysis of the North American Research Committee on MS registry, based on 13,873 cross-sectional surveys, indicated that about half of patients (45.7%) had some degree of tremor and 5.8% had severe tremor [3].

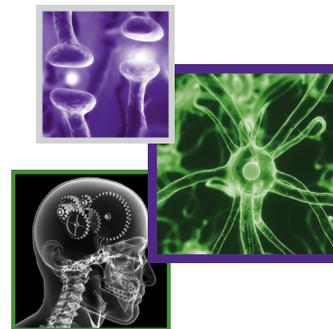
Most MS patients with tremor experience symptoms within 5 years of diagnosis [1], possibly reflecting a biological subtype with predominant brain stem lesions [4]. Tremors can persist for many years or may be 'cured' by subsequent new strategic MS lesions [5]. Tremor frequency has a broad distribution from 1 to 10 Hz, with most in the range of 3.0 to 5.0 Hz; a lower frequency indicates worse tremor.

• Clinical spectrum of tremors in MS

Three major types of MS tremors have been identified (Table 1) [6]. The most frequent variant is intention tremor which is part of the Charcot triad. Titubation is a slow frequency anterior–posterior trunk (and head) tremor which is not pathognomic for MS although other causes are even rarer for this rare syndrome [1]. Postural hand tremor is quite common [1,3], but tends not to be a major complaint according to some authors [4]. As numerous etiologies are possible for unspecific postural tremor, investigations to rule out causes other than MS are strongly recommended for tremors causing complaints.

• Differential diagnosis

MS tremor can arise from an abundance of mostly brain stem lesions. The main differential diagnosis is severe essential tremor. Another important differential diagnosis is Holmes tremor which is characterized by the presence of resting and intention tremor with possible additional postural tremor. It can be unilateral if the lesion is unilateral. The frequency of Holmes tremor is similarly low as severe MS tremor but the most important differential diagnostic feature is resting tremor. A key feature of



KEYWORDS

- deep brain stimulation
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- multiple sclerosis
- paroxysmal dyskinesias
- tremors

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Table 1. Clinical spectrum of tremors in multiple sclerosis.

Definition	Clinical features
Cerebellar (intention) tremor	Pure or predominant intention tremor Uni- or bilateral Frequency below 5 Hz Postural tremor may occur but no tremor at rest
Titubation	Head or trunk tremor Usually involves proximal muscles Occurs only during muscle activity Frequency mainly below 4 Hz No tremor at rest
(High) frequency postural hand tremor	Unspecific postural tremor Mild action tremor Frequency variable Lateralization possible

Data taken with permission from [6].

MS tremors is the absence of rest tremors.

• Treatment of MS tremor

Interventions for severe tremor include Gamma Knife thalamotomy, thalamotomy and deep brain stimulation (DBS). Although prospective controlled studies are lacking, large cohorts have been described for some procedures.

Gamma Knife radiosurgery targeting the ventral intermediate nucleus (VIM) of the thalamus was reported to alleviate MS tremor in six patients, with improvement noted after about 2.5 months [7]. Lesion extension over time is a concern with this procedure.

Thalamotomy had been the mainstay of neurosurgical management of MS tremors until the 1990s; however, DBS now offers a safer alternative [8]. In a comparative study, thalamotomy was found to be more effective than thalamic stimulation in patients with intractable MS tremor (Figure 1), but was associated with more complications including three cases of hemiparesis and seizures versus one case of monoparesis with DBS [9]. Moreover, thalamotomy can only be performed unilaterally.

Geny and coworkers reported improvement at 3 months post-surgery in nine of 13 patients (69%) who underwent thalamic VIM stimulation for MS tremor [10]. The true benefits of this approach were likely to have been underestimated as functional improvement was measured on the Expanded Disability Status Scale (EDSS) which is relatively insensitive to change in mainly arm movements.

In Kiel our group has treated until 2006 14 patients with MS tremor with bilateral stimulation of the thalamic VIM. The cohort had

a mean age of 41.5 ± 3.5 years, mean disease duration of 10.1 ± 1.5 years, and a preoperative EDSS of 7.1 ± 1.0 . Significant improvement of about 30% ($p = 0.003$) on the Fahn–Tolosa–Marin scale was observed at 6 months postoperatively, and persisted at 12 months ($p = 0.0001$; Figure 2). This level of improvement translates into meaningful performance benefits for the patient. DBS in a patient bedridden due to severe titubation (considered by some to be a borderline indication) allowed him to transition into a wheelchair, facilitating participation in social outings and improving his quality of life.

Data regarding the long-term course of MS patients treated with these interventions are limited. In 11 patients with MS tremor treated with thalamic stimulation for >2 years, permanent reduction of tremor in 11 of 18 upper limbs was reported [5]. This finding is consistent with the hypothesis that lesions created along the electrode tract eventually lead to lesion-like effects. In contrast, Hassan and colleagues reported short-lived overall benefit (median 3 months) and shortened life expectancy among a cohort of patients with MS tremor treated with thalamotomy ($n = 6$) or DBS ($n = 3$) [11]. However, the study was uncontrolled, and the life expectancy of similarly affected patients is unknown. It is likely that patients with lower life expectancy were selected for the procedure. Controlled studies in the long-term setting are required.

• Where to stimulate?

Although the traditional target for tremor treatment has been the thalamic VIM [12,13], there was already early support for the zona incerta [14,15]. A kinematic analysis of thalamic versus subthalamic neurostimulation in patients with essential tremor ($n = 10$) and MS tremor ($n = 10$) confirmed greatest efficacy within the subthalamic area covering the posterior zona incerta and radiation prelemniscalis. The best result occurs when stimulation is delivered directly below the lower border of the VIM (Figure 3) [16].

• Transcranial focused ultrasound

Transcranial focused ultrasound is a newer, less invasive method of generating precisely placed focal thermal lesions in the brain. High-intensity focused ultrasound is delivered through the intact cranium using MRI

guidance, heating brain tissue within the focal area up to 64°C. The intensity of ultrasound delivery can be measured and modified as required. Feasibility studies have reported relevant clinical improvement in patients with essential tremor [17–19].

Contralateral hand tremor in essential tremor appears to respond well to this technique but some important issues are unresolved, namely whether lesion extensions and/or bleedings might occur. Due to the unacceptable dysarthria associated with bilateral lesions, transcranial focused ultrasound is restricted to unilateral lesions and precision within the targeted region is limited. The method is experimental and restricted to clinical studies.

• Treatment selection for MS tremor

The level of evidence for and against invasive treatments for MS tremor is low overall (Table 2) [16]. When selecting an intervention, it is important to consider the patient and his/her treatment goal. Patients with bilateral hand tremor aiming at lesional or radiosurgery must choose a side on which the intervention is to be performed. A bilateral procedure is possible only with DBS as all other invasive treatments are irreversible. Patients with midline tremors, for example, titubation or head and voice tremor, must have a bilateral intervention [20].

• Criteria for selecting patients with MS tremor for DBS

In the absence of controlled studies, German consensus statement criteria for selecting patients with MS tremor for DBS are based on expert opinion [21]. Tremor must be predominantly of the distal extremities with significant disability. The diagnosis must be tremor (rhythmicity; tremor frequency >3 Hz; singular frequency peak), not ataxia, and must be unresponsive to medication. The absence of relapse within the previous 12 months is frequently requested, but this is a historical recommendation from the era of lesional surgery [12]. Relative and absolute contraindications for DBS are severe paresis of the trembling extremity, significant psychiatric comorbidity, immunosuppressive therapy (e.g., mitoxantrone), rapidly progressive MS variant with clinical or MRI evidence of relapse and neurosurgical contraindications. Unanswered questions with the procedure include: optimal time to operate; availability of objective tests to differentiate tremor and

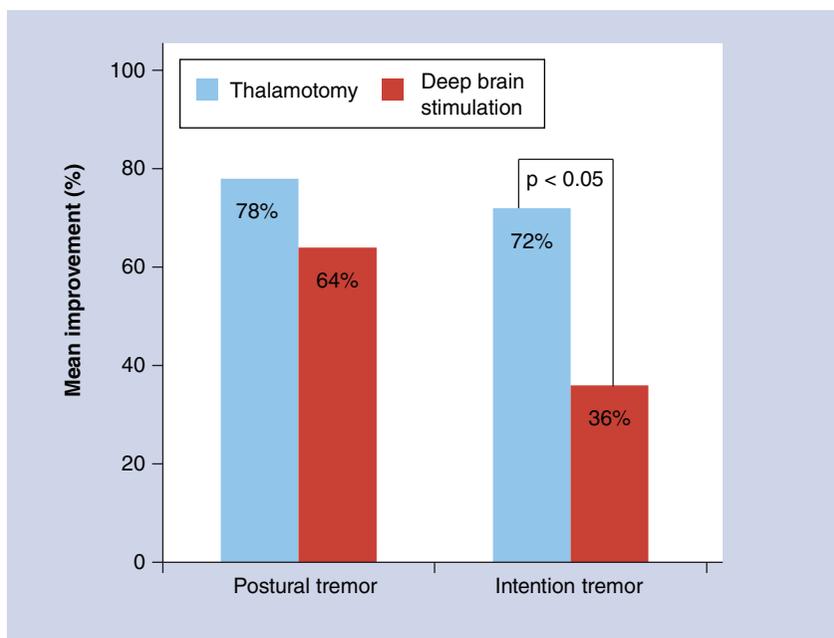


Figure 1. Mean improvement in postural tremor and intention tremor following thalamotomy (n = 10) or deep brain stimulation (n = 10) in patients with intractable multiple sclerosis tremor.

Data taken with permission from [9].

ataxia; effects of immunomodulation; effects of immunosuppression; and long-term effects.

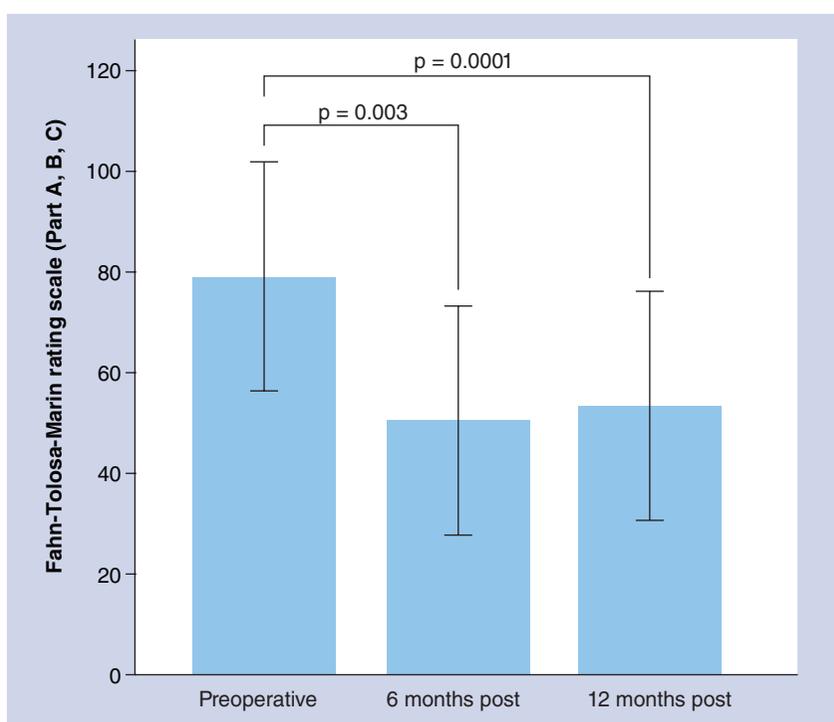


Figure 2. Mean improvement on the Fahn–Tolosa–Marin scale at 6 months and 12 months after bilateral stimulation of the ventral intermediate nucleus in 14 patients with multiple sclerosis tremor.

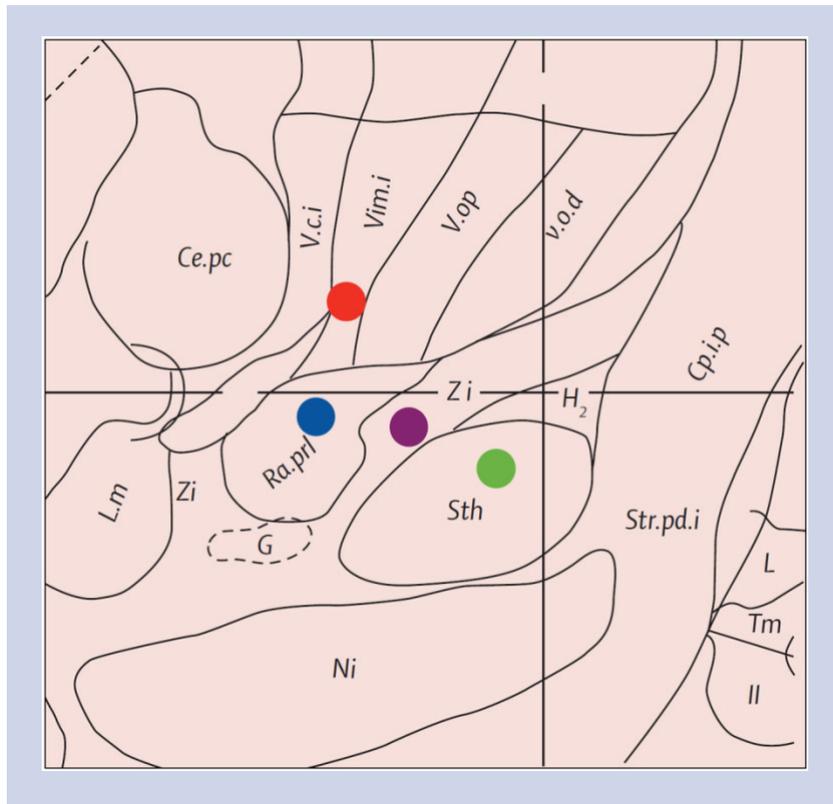


Figure 3. The optimal anatomical target structure for neurostimulation in multiple sclerosis tremor is the subthalamic area covering the posterior zona incerta and radiation prelemniscalis.

Reproduced with permission from [16].

Paroxysmal dyskinesia & other paroxysmal symptoms in multiple sclerosis

Paroxysmal dyskinesias are a group of movement disorders characterized by attacks of

hyperkinesia with intact consciousness [22–25]. MS-induced paroxysmal choreoathetosis, ‘brain stem fits’ [24] or dystonic spasms [25] is a somewhat forgotten albeit genuine diagnosis [26,27]. The condition is characterized by a stereotypical pattern of short duration (seconds to minutes), high frequency attacks, up to 200/day. Consciousness is unaffected and electroencephalogram changes are absent, suggesting a nonepileptic origin. Most cases have dystonic symptomatology, although pain, sensory, ataxic and akinetic symptoms are also possible [28]. The pure dystonic variant has been labeled as tonic spasms [25]. The location of the precipitating lesion remains unknown but clinical findings are compatible with a brain stem origin [24,28]. The differential diagnosis includes all genetic hereditary paroxysmal dyskinesias [29]. MS-induced paroxysmal choreoathetosis responds well to treatment with low doses of carbamazepine. Other antiepileptic drugs (diphenylhydantoin, valproate, phenobarbital, primidone) may also be effective but the evidence is less well documented.

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Table 2. Comparison of invasive treatment for tremors.				
Intervention	Efficacy (evidence)	Safety	Availability	Bilateral procedure
Thalamotomy	C	Surgical intervention	Specialist team	No
Gamma Knife surgery	C	Surgical intervention	Specialist team	No
Deep brain stimulation	C	Surgical intervention	Specialist team	Yes
Focused ultrasound	Experimental	Unknown	Specialist team	No

Level C: Effectively treats contralateral limb tremor in essential tremor that is refractory to medication management, based on case series.
Data taken from [16].

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Pediatric multiple sclerosis: updates in epidemiology, clinical features and management

Sona Narula*

Consensus definitions for acute demyelinating syndromes in children have led to increased recognition of pediatric multiple sclerosis and improved our understanding of its pathogenesis, epidemiology and treatment. An estimated 2–10% of MS patients experience their first clinical symptom in childhood. Multiple genetic and environmental risk factors have been identified in the pathogenesis of pediatric MS, although further research to determine their interplay is required. Clinical trials of emerging disease-modifying therapies in children are nearing completion. Additional treatment options are expected to bring associated challenges. As pediatric MS remains relatively uncommon overall, international collaboration is essential to facilitate research.

Definition of pediatric MS

Pediatric multiple sclerosis (MS) is a CNS inflammatory disorder that can affect young children and adolescents. A consensus definition has been proposed by the international pediatric MS study group [1] based on confirmation of CNS inflammation separated in time and space. Although the 2010 revised McDonald criteria permit diagnosis of pediatric MS [2], caution is advised in prepubertal children as the positive predictive value has been found to be low in children less than 11 years of age [3].

Clinical features of pediatric MS

Presenting symptoms of MS in children are heterogeneous, and include paresthesias, cranial nerve palsies, optic neuritis, bowel/bladder dysfunction, weakness and ataxia. Symptoms referable to demyelination typically last at least 24 h. Cognitive disability is prominent in children within the first few years after diagnosis [4]. Specific areas of concern include memory, executive function, processing speed and attention, and language [5]. Depression and fatigue, which can exacerbate cognitive impairment, are also common [4,6].

Although pediatric MS nearly always has a relapsing-remitting course at onset, children's physical recovery from relapse is generally excellent and complete, with minimal accrual of physical disability [7]. Children take 10–20 years longer than adults to reach secondary progressive MS, but reach it at a younger age due to the earlier onset [8].

Radiological features of pediatric MS

Compared with adults, children tend to have a higher overall volume of brain lesions early in the disease course with a proclivity for infratentorial regions [9]. Pediatric MS patients also show reduced thalamic volume, age-expected whole brain growth and head size compared with their counterparts without MS [10–12]. Radiological red flags that suggest diagnoses other than MS or demyelinating conditions include:

- Meningeal enhancement (→ consider vasculitis or infection);
- Symmetric or confluent lesions (→ consider leukodystrophies or metabolic processes);

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KEYWORDS

- diagnosis • management
- pediatric multiple sclerosis
- randomized controlled trials • risk factors

Box 1. Differential diagnosis of acute demyelination in children.

- Infections (bacterial, viral, fungal or parasitic infections)
- Rheumatological disorders
- Malignancy
- Autoimmune encephalopathies
- Macrophage activation syndromes
- Metabolic or mitochondrial disease
- Vascular diseases
- Nutritional deficiencies

Data adapted from [15].

- Complete ring enhancement (→ consider infection).

Cerebrospinal fluid profile

At diagnosis of pediatric MS, mild-to-moderate pleocytosis in cerebrospinal fluid is common; cell counts greater than 50 cell/ μ l are unusual. Oligoclonal bands are typically positive in post-pubertal children (87–92%), although this can depend on the methodology used for analysis. Prepubertal MS tends to be associated with a higher white blood count in cerebrospinal fluid, a higher proportion of neutrophils and a lower likelihood of positive oligoclonal bands [13].

Prepubertal MS

Prepubertal MS is a rare diagnosis, comprising less than 1% of all cases. Children in this age group are more likely to present with polysymptomatic attacks and more prominent motor and brainstem involvement (diplopia, facial weakness), sphincter dysfunction and cognitive disturbances. The gender ratio is thought to be equal [14]. Diagnosis is often delayed because children are less able to articulate subtle symptoms such as paresthesias or mild unilateral vision loss. Large ill-defined infratentorial lesions on MRI scans are a common feature. The presence of any of the following clinical signs and symptoms suggests a diagnosis other than MS:

- Progressive course from onset;
- Refractory seizures;
- Peripheral nerve involvement;
- Systemic symptoms (headache, joint pain, fever);
- Severe psychosis.

In pediatric patients with atypical clinical features, the differential diagnosis of acute

demyelination includes many other conditions (Box 1). In each diagnostic category, additional investigations may be required to arrive at a definitive diagnosis [15].

Incidence & prevalence of pediatric MS

An estimated 2–10% of all MS patients have their first clinical symptom during childhood. The actual prevalence of pediatric MS is difficult to determine because of historical variation in the definitions of inflammatory demyelinating disorders, small sample sizes and limited reporting. The increased incidence of pediatric MS in the past few years likely reflects better recognition of the condition through global use of consensus definitions, although environmental factors may also have a role.

Epidemiology of pediatric MS

Pediatric MS epidemiology encompasses a range of genetic and environmental risk factors. The level of risk conveyed by environmental factors may differ depending on a person's genetic background. Awareness of the risk factors can increase understanding of the disease pathogenesis and help identify strategies for risk modification and treatment.

• Hormonal influence

Although the mechanisms behind the influence of hormones on the pathogenesis of pediatric MS are uncertain, evidence suggests a role. MS incidence increases in females post puberty [14,16], and the relapse rate increases during the perimenarche period [17]. Later age at menarche was associated with a lower risk of subsequent MS diagnosis in patients with an acute demyelinating syndrome [18].

• Obesity

Childhood and adolescent obesity increases the risk of MS in adults [19,20]. Obesity is also associated with a higher risk of pediatric MS in girls [21], possibly due to fat-related chronic inflammation, increased estrogenic exposure and/or increased production and release of pro-inflammatory cytokines. Obese people may have lower levels of vitamin D metabolites due to their deposition in body fat compartments [22].

• Vitamin D deficiency

Higher serum vitamin D levels are associated with a lower relapse rate in pediatric-onset MS, with the relapse rate decreasing by 34% for every

10 ng/ml increase in the vitamin D level [23]. Although it is uncertain whether supplementation has the same effect as naturally occurring vitamin D, the low level of associated risk with supplementation suggests a positive risk:benefit ratio. Moreover, higher vitamin D levels have been associated with lower risks of accrual of T2 or enhancing lesions on MRI [24].

- **Smoking**

The risk of MS is about 1.5-times greater in smokers than in nonsmokers, and duration and intensity of smoking are independent contributors to risk [25]. In children, exposure to passive smoke has been associated with a higher risk of developing MS [26]. It has been posited that irritation in the lungs may create autoimmunity against proteins which cross-react with CNS antigens.

- **Viral exposures**

Epstein–Barr virus (EBV) seropositivity is strongly associated with MS risk, with a meta-analysis indicating a 13.5-fold higher risk in seropositive versus seronegative individuals [27]. Several studies have reported an increase in EBV antibody titers prior to MS diagnosis. In contrast, remote cytomegalovirus infection has been associated with decreased MS risk [28,29].

- **Genetics**

Concordance rates among monozygotic twins (17–30%), dizygotic twins (2–7%) and first degree relatives (3–5%) pointed to the influence of genetics on MS pathogenesis. The human leukocyte antigen (HLA) *DRB1*15* allele has been associated with increased susceptibility of MS, whereas *HLA-A*02* may be protective [30]. Genome-wide association studies have identified a number of genetic loci outside the HLA complex that contribute to MS risk in both children and adults [31,32].

- **Combined genetic & environmental risk**

Adults positive for *HLA-DRB1*15*, negative for *HLA-A*02*, and with high EBNA titers (exposure to EBV) had a 16-fold higher risk for MS than those who did not carry any of those factors [33]. In a study of children with an incident demyelinating attack, 57% of those with the presence of *HLA-DRB1*15*, remote EBV infection and low vitamin D levels were ultimately confirmed to have MS, whereas risk for children without these factors was 5% [34].

Management of pediatric MS

At the time of an acute demyelinating attack, methylprednisolone use hastens clinical recovery but does not influence the disease course; its primary indication is in cases where symptoms impair function or cause discomfort. To limit long-term disability, disease-modifying therapy should be initiated as soon as diagnosis is confirmed. First-line disease-modifying therapies for use in pediatric MS are glatiramer acetate and IFN- β -1a and -1b [35]. A significant proportion of patients will need to transition from first- to second-line therapy within the first few years after diagnosis due to inadequate response or poor tolerance [36]. Second-line therapies for pediatric MS are natalizumab, cyclophosphamide and rituximab. Some specific challenges with medication adherence in children include needle-phobia, potential side effects (injection-site reactions with glatiramer acetate; flu-like symptoms with interferon) and cognitive impairment (forget to take medications).

A multidisciplinary care team is recommended to address the various comorbidities of pediatric MS including physical and cognitive symptoms. As well as pharmacotherapy, children with MS require physical therapy, occupational therapy, social work and psychology.

- **Emerging therapies**

Randomized, controlled clinical trials are currently underway for oral therapies in pediatric MS (10–17 years). The PARADIGMS study is evaluating the safety and efficacy of fingolimod versus IFN- β -1a (ClinicalTrials.gov identifier: NCT01892722) [37], and TERIKIDS is comparing teriflunomide with placebo (ClinicalTrials.gov identifier: NCT02201108) [38].

- **Symptomatic treatments**

Fatigue in pediatric MS patients is usually treated with nonpharmacological interventions such as exercise and sleep routine modification. For significant fatigue affecting day-to-day functioning, medications such as modafinil and amantadine may be considered.

The high frequency of depression in pediatric MS underlies the importance of partnering with psychology and psychiatry to manage patients in this age group. Neuropsychiatric testing should be performed as needed.

Gabapentin is often used to treat neuropathic pain based on evidence for its use in other pediatric disorders.

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IL4I1 decreases inflammation and promotes CNS repair in models of multiple sclerosis

Our panel of experts highlights the most important research articles across the spectrum of topics relevant to the field of regenerative medicine

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IL-4-induced 1 (IL4I1) decreases inflammation and promotes CNS repair in models of MS.

Evaluation of: Psachoulia K, Chamberlain KA, Heo D et al. IL4I1 augments CNS remyelination and axonal protection by modulating T-cell driven inflammation. *Brain* 139(Pt 12), 3121–3136 (2016).

Multiple sclerosis (MS) is a highly complex disease involving inflammation, demyelination and spontaneous demyelination–remyelination episodes which ultimately fail during the course of the disease. The prognosis for patients is often bleak. Molecular evidence has demonstrated that activated inflammatory mediators are important for the differentiation of oligodendrocyte progenitors into functional myelin. In the paper published in *Brain* under discussion, the researchers categorized the role of alternatively activated macrophages (AAM) versus classically activated macrophages (CAM) as being beneficial for the promotion of remyelination. There is distinct temporal activation of macrophages within lesions of the CNS. During CNS remyelination and tissue repair processes, inflammatory processes are tightly regulated. IL4I1 is highly expressed during CNS remyelination. IL4I1 is expressed by immune cells, is stimulated by IL-4 and has immunomodulatory functions in various tumors and bacterial infections. The authors set out to determine whether IL4I1 affects remyelination or protects axonal damage in a mouse model of MS.

Initial studies in this area looked at transcriptome analysis of microdissected rat CNS lesions and found IL4I1 to be associated and upregulated with CNS remyelination at 14 days post-lesion, which is when inflammation is typically resolved and spontaneous remyelination begins to occur. Lysolecithin focal lesions were then performed in a mouse model and characterized. Oligodendrocyte precursor cell recruitment occurred at 3 days post-lesion and differentiation occurred at 10 days post-lesion. Completion of remyelination was at 20 days post-lesion. Interestingly, polymerase chain reaction analysis determined IL4I1 expression was induced at 10 days, post-lesion, and decreased by 20 days, after lesion. *In situ* hybridization determined that IL4I1 was detected in cells resembling macrophages. To determine the signaling in macrophages, they induced primary microglia and macrophage cell lines with IL4 and found that IL4I1 expression was increased. In their IL4 knockout mouse model of demyelination, IL4I1 was reduced as compared with wild type. So IL4I1 is dependent on IL4 receptor activation and is important in AAM. Addition of IL4I1 to oligodendrocyte lineage cells did not affect the number of precursors or oligodendrocytes so it is not a direct link between IL4I1 and maturation.

Modulation of inflammation was then assessed using the focal demyelination model of MS. They utilized IL4I1 knockout animals. The lack of IL4I1 created a prolonged activation of macrophages which is typically reduced by 10–20 days post-lesion. Animals

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without IL4I1 active had an induction of gliosis also post-lesion. Variability across the different mice made it difficult for the researchers to make concrete conclusions on the role of IL4I1 and AAM. Transition from high CAM/AAM to low CAM/AAM is important for remyelination to be successful. In wild-type animals with lesions, the ratio switches between 5 and 20 days post-lesion, which is a shift in the acute inflammation. In lesions of IL4I1 knockout mice, the ratio remains elevated at 20 days post-lesion. Since IL4I1 is a secreted enzyme, the researchers injected recombinant protein into the lesions of wild-type mice, and determined macrophage density to be high 5 days post-lesion and reduced by 10 and 20 days post-lesion. This injection must have had a delay in the CAM distribution within the lesion environment so IL4I1 may indirectly influence macrophage activation.

Importantly, the researchers then assessed the effect that IL4I1 has on remyelination. Immunohistochemistry revealed no difference in early oligodendrocyte markers in the IL4I1 knockout mice with lesions but the mature oligodendrocytes were reduced in the IL4I1 knockout mice. The mature oligodendrocytes were typically found in the periphery of lesions, suggesting they may have undergone cell death. Lesions of IL4I1 knockout mice also had reduced remyelinated axons as demonstrated by electron microscopy. Dystrophic axons were also present in lesions with deficiency in IL4I1 signaling. Administration of IL4I1 at 5 days post-lesion revealed oligodendrocyte precursor cell numbers to be significantly increased. Mature oligodendrocytes were also significantly increased with IL4I1 treatment in lesions. IL4 knockout mice similarly have reduced mature oligodendrocytes and remyelination with axonal dystrophy after lesioning. Since IL4I1 is downstream of IL4 receptor activation, it was importantly assessed whether treatment with recombinant IL4I1 could rescue this phenotype. Induction of remyelination and oligodendrocyte density was increased with administration of IL4I1 into IL4 knockout lesioned mice.

This current research points to the role of IL4I1 in modulating inflammation to promote remyelination. The researchers assessed proinflammatory factors in astrocyte and macrophage cell cultures and their response to IL4I1 administration. They determined that IL4I1 did not directly modulate macrophage and astrocytic responses. Therefore, IL4I1 may regulate T-cell activity so they assessed the environment of the spinal cord lesions. They found that IL4I1 reduced IFN- γ and IL-17 expression but did not have an effect on IL-4. This points to IL4I1 as an important regulator in T-helper 1 and Th17 activation. The researchers notably utilized an autoimmune inflammatory model of MS, experimental autoimmune encephalomyelitis. Animals received IL4I1 after the onset of the disease. Animals with IL4I1 continued the course of the disease, however, the animals recovered from paralysis over time, whereas the control mice did not. This suggests that the treatment reduces the disease severity which the authors attributed to a reduction in Th1, Th17 and Th2 cell expansion in the spinal cord and spleen of the mice due to fluorescent activated cell sorting analysis postdisease. Further, axonal injury was reduced in animals treated with IL4I1.

This manuscript proves IL4I1 to be an important regulator in inflammation and promotes the spontaneous remyelination in an animal model of MS. Importantly, the researchers utilized a therapeutically relevant treatment paradigm. This provides important evidence to enhance the potential of moving into clinical trials for the treatment of MS.

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Neuroimmunology and multiple sclerosis: an interview with Katerina Akassoglou



As part of Neurology Central's Spotlight on neuroimmunology, Lauren Pulling (Editor, Neurology Central) spoke to Katerina Akassoglou about her pioneering work on the interactions of the immune and nervous systems in neurologic disease. Dr Akassoglou's work centers on the leakage of the blood-brain barrier in disease and injury, and the mechanisms by which blood proteins subsequently activate immune cells that attack the brain. Of particular note is her work on the role of the blood protein fibrinogen in multiple sclerosis – research that she hopes will one day lead to an effective treatment for patients. In this interview, Dr Akassoglou discusses her research, as well as the key challenges in this exciting area of neuroscience and her hopes for the field.

Dr Akassoglou is primarily a Senior Investigator at the Gladstone Institutes (CA, USA) and a Professor of neurology at the University of California, San Francisco (UCSF; CA, USA). She is also an Associate Adjunct Professor of Pharmacology at the University of California, San Diego (CA, USA), and directs the Gladstone/UCSF Center for In Vivo Imaging Research.

Q First, could you tell us a little about your background? How did you come to work in neuroimmunology?

I became interested in neuroimmunology early on. I pursued my PhD in an immunology lab at the Hellenic Pasteur Institute (Athens, Greece), studying the cytokine tumor necrosis factor (TNF), under the direction of George Kollias and Lesley Probert. The lab had made several transgenic mice expressing TNF, and all these mice developed arthritis. However, there was one transgenic line that was paralyzed without any symptoms of arthritis. My PhD project was to find out why TNF caused paralysis in this line. I made the unexpected discovery that, in this particular line, TNF was expressed only in the brain and spinal cord. With the expert guidance of Hans Lassmann at the University of Vienna (Austria), we discovered that expression of TNF in the brain was sufficient to activate brain immune cells and cause MS-like symptoms, such as leakage of blood in the brain and loss of myelin. It was an eye-opener that autoimmunity is not the only way to induce loss of

myelin, but other mechanisms like activation of brain immune cells appeared to be potent drivers of disease. In 1998, I was fortunate to receive the Women In Neuroimmunology Award by Cedric Raine and the International Society for Neuroimmunology for my PhD work. It truly was an unexpected honor for a graduate student like myself.

Neuroimmunology is perhaps one of the most multidisciplinary fields of study that requires training in multiple fields. During my PhD training, I made the observation that activation of brain immune cells strongly correlated with leakage of blood in the brain. I was curious as to whether blood in the brain could be responsible for activating the brain immune cells and cause damage. To obtain training in blood proteins, I pursued my postdoctoral studies at The Rockefeller University (NY, USA) under the guidance of Sidney Strickland. The blood protein fibrinogen was already recognized as a marker of disruption of the blood-brain barrier (BBB), but no one had actually asked about its role in brain diseases. Was it a cause of the

disease or a consequence? We made the unanticipated discovery that fibrinogen was required for regeneration of the peripheral nerve. This was the first time that fibrinogen knock-out mice had been tested for their neurological functions. After having completed training in immunology, neurobiology and hematology, I was ready to study in my own lab how fibrinogen affects brain functions. Indeed, we showed that, when fibrinogen gets into the brain, it activates microglia, the brain's immune cells, to become pro-inflammatory cells, promoting autoimmune responses and neuronal damage.

Q What are your lab's current research focuses?

We focus on the molecular mechanisms that control communications among the brain, immune system and blood vessels. We continue to study fibrinogen and other blood proteins and their effects on microglia in mouse models of MS that we developed. We want to understand those interactions in mouse brains and spinal cords and learn what happens when the BBB is disrupted and as the process of demyelination and neurodegeneration begins. We recently found a way that we might be able to block the effects of fibrinogen in the brain. We made other significant discoveries, including a fascinating relationship between astrocyte activation and neuronal activity and remodeling of the nuclear pore complex. We are also looking beyond fibrinogen to its downstream pathways directly linked to neurodegeneration. For example, we are using state-of-the-art genomic and proteomic technologies to discover new pathways that damage neurons.

We have also invested a great deal in imaging, particularly high resolution *in vivo* imaging. We knew the microglia were dynamic cells, but we needed the ability to see them in action in living animals. So we developed methods to image the neurovascular interface *in vivo* in transgenic mice. We use high-resolution two-photon microscopy and fluorescently labeled microglia, T cells and fibrinogen. With this procedure, we can watch the whole disease process as it moves from a normal brain to full-blown autoimmune disease. We've made some surprising discoveries. For example, in MS, microglia change shape and cluster around blood vessels early on in the disease course. This finding supports the theory that disruption of the BBB and leakage of blood into the brain may occur before other symptoms of disease.

Q Could you talk us through your work on the role of fibrinogen in MS?

As I mentioned, we showed that when the BBB is disrupted, fibrinogen leaks into the brain, where it binds to receptors of microglia, astrocytes and neurons to induce inflammation, axonal damage and glial scar formation. As a result, axons are damaged. Fibrinogen is abundant in MS and is a major culprit of the disease. Indeed, fibrinogen is present in human MS lesions at varying degrees throughout the course of disease, including normal appearing white matter, early lesions, chronic active and chronic inactive lesions.

Our studies have shown that fibrinogen in the brain enables autoimmunity and recruits macrophages to injury sites. It creates a chemotactic gene signature in microglia to activate and recruit myelin-specific T cells and peripheral macrophages to the CNS, leading to demyelination. We showed that we could increase repair to the nervous system and protect axons from damage by depleting fibrinogen. We also learned that fibrinogen binds to the complement receptor 3 on microglia, causing them to release toxic reactive oxygen molecules. If we inhibited the binding, the microglia were not activated, and the nerve was not damaged.

Q Do you anticipate that your findings could lead to novel treatments for patients?

We are committed to developing new therapies for neurological diseases, and our focus has been on targeting fibrinogen in the CNS. We are looking at ways to target the harmful activities of fibrinogen in the brain without affecting its function in the blood. Of course, this is a tricky thing to attempt. Fibrinogen is essential for blood clotting, so we cannot simply eliminate it completely. However, we hope to find ways to separate the two activities. That is, we want to block the deleterious effects of fibrinogen in the CNS without interfering with its coagulation activity. We already showed with genetic tools that this separation is feasible, and pharmacologic tools to selectively target the inflammatory functions of fibrin in the brain are under development.

Another goal might be to use blood-clotting proteins as biomarkers for MS, which would allow us to predict the disease course of patients to study and treat them more effectively and to facilitate future development of new therapies. We also developed a molecular probe that detects lesions early in MS. With this probe, we

showed that coagulation is activated in the CNS in animal models of MS and stroke. The probe can also be developed for magnetic resonance imaging, and so it may have clinical applications.

Q Do you think your findings concerning leakage of the BBB and activation of the innate immune response in MS could translate across to other neurodegenerative diseases?

Yes, I do. Fibrinogen is not just found in brains of patients with MS. It is found in any neurological disease or trauma with disrupted BBB. For example, it is found in the brains of patients with Alzheimer's disease, ischemia, spinal cord injury, traumatic brain injury, stroke, schizophrenia, HIV encephalopathy and potentially normal aging. Further studies might benefit these patients as well. Thus, we suspect that the leakage of blood into the brain and activation of the innate immune response are common threads in neurological diseases.

Q What are the key challenges in investigating the role of the immune system in neurological disease? How did/do you overcome these?

One of the challenges was how to actually visualize the sequence of events occurring after injury in living organisms and not rely on dogma for how brain diseases start and progress. We developed methods for *in vivo* microscopy so that we could follow the movement of immune cells in the brain. These involve high-resolution two-photon microscopy and fluorescent labelling of cells and proteins. It is important to know what happens in the brain when the disease starts and progresses and study these early mechanisms together with their more obvious consequences.

The ultimate challenge will be to translate these findings from mice into human studies. Targeting the immune system in MS has been one of the biggest successes in drug discovery leading to several FDA-approved drugs in the past 10 years. In contrast, other neurological diseases, such as Alzheimer's disease, have not had

similar translational success yet. Indeed, many recent clinical trials based on good results in mouse studies have failed in humans, and many scientists now wonder if mouse models are only partially recapitulating features of these diseases. It is timely to look for therapeutic targets not only in the brain, but also in the immune system and the blood, even for diseases not traditionally classified as 'neuroimmune'.

Q More broadly, what do you think are the key questions to be addressed in the field of neurological disease in the next 5–10 years?

Traditionally, diseases have been classified as neurodegenerative (for example, Alzheimer's), inflammatory (for example, MS), and vascular (for example, stroke). But more recently, scientists have begun to look at these diseases in the context of the complex relationships between the brain, immune and vascular systems. There is now a search for common threads among these diseases. We will need to re-evaluate our understanding of the causes and signals that regulate disease onset and progression, and recognize that neurological disorders cannot be described in isolation.

Tragically, effective therapies are lacking for major neurologic diseases. Alzheimer's disease was first described more than 100 years ago, and our society and those of many countries in the world are aging – the greatest risk factor for neurologic disease. An integrated approach is more likely to lead to new insights about the brain and better ways to treat its diseases. Neuroimmunology is uniquely positioned to play a central role for the understanding of fundamental mechanisms of all brain diseases and for the discovery of new therapies. I am extremely encouraged that the scientific community is increasingly recognizing this potential.

Disclaimer

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