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The usefulness of immunotherapy in pediatric neurodegenerative disorders: A systematic review of literature data

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Immunotherapeutic strategies to treat neurodegenerative disorders have inspired the scientific community. The aim of our review is to address the translational aspects of neuroimmunology to describe the efficacy of immunotherapy in the treatment of pediatric neurodegenerative disorders. In the studies we analyzed IVIG were found to be efficient in the treatment of post-streptococcal neurodegenerative disorders, even if in PANDAS, plasma-exchange (PE) showed a higher efficiency. IVIG were also successfully used in ADEM and Guillan-Barré syndrome. In Sydenham Chorea the use of methylprednisolone was found in most cases as efficient as IVIG, while in Tourette's Syndrome, Colecoxib was successfully used in one patient. Pediatric Multiple Sclerosis seems to respond better to immunosuppressant agents (Mitoxantrone, Cyclophosphamide, Natalizumab), as well as Neuromyelitis optica (Rituximab, Mycofenolate). The importance of this review relies in the attempt to draw standardized guidelines for immunotherapy in pediatric neurodegeneratve disorders

Introduction

Since mouse models of Alzheimer disease were successfully treated using immunotherapeutic strategies, other neurodegenerative disorders as well as autoimmune disorders, neoplastic and atherosclerotic conditions also became subjects to this challenge. The cross-talk between nervous system and immune system is being studied thoroughly and is considered an important contributor of pathogenesis of these disorders resulting in immune-related therapeutic strategies. The most used treatment for immuno-mediated neurodegenerative disorders in childhood is referable on the use of immunoglobulins. Nevertheless, the difficulty in providing this kind of treatment may affect the possibility of this therapeutic approach on a large scale of neurodegenerative patients.

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The aim of our review is to address the translational aspects of neuroimmunology, in order to update clinicians on basic research discoveries that will have therapeutic clinical efficacy and to study the efficacy of alternative treatments to immunoglobulins, which may be more easily available on large scale, for children affected by neurodegenerative disorders.

Methods

The major studies, clinical trials, case reports and reviews on the use of immunotherapy in pediatric neurodegenerative disorders, with or without statistical meta-analysis, were selected. Those reporting evidence of one or more immunotherapeutic approaches in association with other standardized therapies were considered (outcome). Studies that assessed the efficacy of therapeutic interventions different from immunotherapy in the studied neurodegenerative disorders were excluded.

Given the lack of an electronic database that contains all publications of all medical journals and that a restriction of only one database could be associated with a systematic bias, it was necessary to combine multiple databases for a comprehensive literature search. For this reason, an electronic literature search was carried out in MEDLINE via PubMed interface, SCOPUS, Google Scholar, the Cochrane Library for all articles published from inception to February 2015. Database-specific search strings were developed and included search terms describing immunotherapy (population/exposure/intervention) and pediatric neurodegenerative disorders (study design/description of cases). A combination of medical subject headings and keywords was used. Titles and abstracts of identified papers were screened by 2 independent reviewers to determine whether they met the eligibility criteria of interest to develop our review. Subsequently, full texts of the remaining articles were independently retrieved by the 2 reviewers for eligibility.

The immune response in the Nervous System and some neurodegenerative disorders

Although the central nervous system (CNS) is considered an immune-privileged environment, it is proved that the innate

immunity recruits adaptive immunity cells through secretions of various cytokines and chemokines that induce expression of adhesion molecules on the blood-brain-barrier and co-stimulatory molecules on microglia.[1] Innate immune responses not only develops in response to exogenous triggers such as viral and bacterial components through conserved pattern-recognition receptors (PRRs), including toll-like receptors (TLRs), but is also activated endogenously by activation of danger-associated molecular patterns (DAMPs), some of which, such as heat shock proteins (HSP), uric acid, chromatin, adenosin and ATP, high mobility group box chromosomal protein-1 (HMGB-1), hyaluronan, fibrinogen and aggregated, modified or misfolded proteins such as amyloid-β (Ab), apha-synuclein and microtubule associated protein-tau.[3] Microglia, astrocytes, oligodendrocytes and neurons are shown to express TLRs 2,3 and 4.[2] Activated TLRs produce pro-inflammatory cytokines that lead to neuronal damage of the nearby environment. It has been demonstrated that TLRs 2 and 4 are responsible in neurodegenerative processes since mice models deficient in these TLRs, exhibit reduced levels of pro-inflammatory cytokines and milder clinical disease following traumatic brain injury or middle cerebral artery occlusion.[3] Moreover TLR2, TLR3 and TLR4 have been found increased in Parkinson disease (PD), stroke and Amyotrophic Lateral Sclerosis (ALS) models and Alzheimer disease (AD).[4,5] TLR expression was also found increased in Multiple Sclerosis (MS) and in samples of experimental autoimmune encephalitis (EAE), in which it was found that TLR-4 knockout mice were resistant to EAE and TLR9-deficient mice developed less severe clinical inflammation.[6] This involvement potentiates TLRs and consequent immune processes as targets for therapeutic strategy in CNS diseases.

An accelerated accumulation of advanced glycation end-products (AGE) has been observed in MS and AD, as well as aging. Since the receptor for AGE (RAGE) is increased following oxidative stress, immune and/or inflammatory responses, and altered cell functions, AGE accumulation is also a trigger for these processes. Followed by RAGE induction pro-inflammatory cytokines and free radicals are secreted, perpetuating the damage process. An increase of RAGE expression on neurons and astrocytes is detected in AD as well as on oligodendrocytes in response to stress in MS.[7] HMGB1, a ligand of RAGE and DAMP, increases in MS lesions.[8]

Activation of innate immunity leads to the production of pro-inflammatory cytokines such as tumor necrosis factor-a (TNF-a) and interleukin (IL)-6, and of the chemokine CXCL8, seen in many neurodegenerative disorders. Downstream effects, including an increase in caspase activity, of intracellular calcium levels and of the production of reactive oxygen species (ROS) have been implicated in AD, systemic lupus erythematosus (SLE), traumatic brain injury (TBI) and Huntington's chorea.[1]

Also the complement system, is another component of the innate immunity involved in the pathogenesis of neurodegenerative disorders. Most complement components and receptors are expressed by astrocytes, microglia and neurons. Increased expression of these proteins have been found increased in the CNS in AD, ALS, SLE, Huntington's chorea, MS, PD and cerebral stroke.[9] Literature data have shown the presence of antibodies to neurons and altered lymphocyte functions are seen in some neurodegenerative disorders.[10,11]

The same immunopathogenesis is also considered for pediatric CNS disorders and immunotherapeutic strategies have long been used in these disorders. For example, some movement disorders occur as a result of antibodies to group A β-hemolytic streptococcal infections that cross-react with human basal ganglia tissue, resulting in motor and psychiatric symptoms.[11]

Altered and elevated T-cell responses to CNS antigens plus shifts in the ratio of CD4+ to CD8+ cells both in the CNS and periphery in neurodegenerative disorders are evidences for involvement of cellular immune. However, T cells directed to myelin and neural antigens are also detected in healthy individuals.[12] Altered ratio of CD4+ to CD8+ T cells is observed in AD, ALS and traumatic brain injury.[13-15] It is suspected that the neural damage in MS, is mediated through CD8+ T cells that act in contrast with neurons. Also, B cells, and CD4+, CD8+ T cells can play a role in MS by the close association of T cells expressing TNF-related apoptosis-inducing ligand (TRAIL) with dying spinal motor neurons.[16] However, protection and repair processes are also mediated by T cells since for example, CD4+ T cells are found to play protective role in mouse models of ALS.[17] Also brain-derived neurotrophic factors, produced by T cells and other inflammatory cells in brain lesions of MS and ADEM patients are basically neuroprotective.[18] **Table 1** summarizes the immunopathogenic features of those neurodegenerative disorders treated in this paper.

Immunotherapeutic approaches to Pediatric Neurodegenerative disorders based on the immunopathological aspects of these diseases

The post-streptococcal movement disorders spectrum (PSMDs)

Sydenham's Chorea (SC) also known as St Vitus dance, chorea minor and chorea rheumatica was first identified by Thomas Sydenham in 1686 and described as characterized by abrupt, irregular involuntary movements and alterations in behavior.[19] Later in 1802, an association between SC and rheumatic fever was found and further studies also recognized their common trigger in the streptococcal infection. Antibiotic treatments for streptococcal infections led to a decline in the incidence of SC, however the disease re-emerged in the 1980s with a different phenotype. An outbreak of streptococcal tonsillitis lead to development of sudden movement disorders characterized as tics.[20]

Preservative behavioral changes in SC were first noticed by Sir William Osler.[21] Depression, anxiety, obsessive-compulsive behavior and attention deficit hyperactivity disorder (ADHD) are the behavioral changes in Sydenham's chorea initially dubbed as *choreic temperament*.[22] With the re-emergence of children with sudden-onset tics and behavioral changes in 1980s, Swedo et al. evaluated fifty children with these symptoms following a group A β-hemolytic streptococcal infection, introducing the novel term of "pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)". PANDAS patients are

Table 1. description of the immunopathogenic features of pediatric neurodegenerative disorders

Immune molecule involved in the pathogenesis	Disease in which it has been recognized	Innate vs Acquired immune system (IS)	Mechanism of Action	References
TLR2, 3, 4	PD[*], ALS[**], AD[°]	Innate IS	Trigger to start innative immune response	Okun E. et al, 2009 (6); Letiembre M et al, 2009 (7); Jackson AC et al., 2006 (8)
TLR4, 9	MS[''], EAE[¨]	Innate IS	Trigger to start innative immune response	Bsibsi M et al, 2002 (4); Prinz M et al, 2006 (11); van Noort JM, 2007 (12)
NLRs[$]	AD[°]	Innate IS	Recognition of intracellular invaders	Visser L et al, 2006 (14)
RAGE[%]	MS['']	Innate IS	Increased activity following oxidative stress, immune and/or inflammatory responses, and upon altered cell functions	Qin J et al, 2008 (16); Sternberg Z, 2008 (17)
Adenosine receptors	AD[°]	Innate IS	Regulation of inflammation by modulation of cytokine release	van der Putten C, 2009 (19); Salminen A, 2009 (20)
Complement fragment C1q, C3, C4	PD[*], ALS[**], AD[°], MS[''], Traumatic brain injury, SLE[¢], Huntington's chorea	Innate IS	Opsonization, activation of acquired immune system, contribution in inflammatory processes leading to gliosis, axonal death and basal gangla abnormalities	Bonifati DM, 2007 (21); Gasque P, 2000 (22)
ABGA[°°]	PANDAS[¥], SC[£], TS[€]	Acquired IS	Molecular mimicry, cross-reaction with neuronal antigens	Church A, 2004 (58); Pavone P et al, 2004 (59); Gause C et al, 2009 (60); Morer A et al, 2008 (61)
aPL[Æ]	SLE[¢], APS[¶]	Acquired IS	Molecular mimicry, cross-reaction with neuronal antigens	Peluso S et al, 2012 (88); Lazurova I et al, 2007 (89)
anti-MOG[⌘]	ADEM[~]	Acquired IS	Molecular mimicry, cross-reaction with neuronal antigens	O'Connor KC et al, 2007 (98)
T-lymphocytes subsets B-lymphocytes anti-MOG[⌘]	MS['']	Innate IS and Acquired IS	Production of proinflammatory cytokines; Interaction with metalloproteinases (MMPs); Activation of proinflammatory humoral immunity; Molecular mimicry, cross-reaction with neuronal antigens	Frohman EM et al, 2006 (141); Charo IF et al, 2006 (142); Hemmer B et al, 2006 (143); Baranzini SE et al, 1999 (144); Colombo M et al, 2000 (145); Krumbholz M et al, 2005 (146); Cepok S et al, 2005 (147); Genain CP et al, 1999 (148); Berger T et al, 2003 (149); Reindl M et al (150)
Anti-gangliosides antibodies T-lymphocytes subsets	GBS[⊠]	Acquired IS	Molecular mimicry, cross-reaction with neuronal antigens; Production of proinflammatory cytokines	Kuwabara S et al, 2004 (211); Magira EE et al, 2003 (212); Hartung HP et al, 2002 (213)

*PD: Parkinson Disease.
**ALS: Amyotrophic Lateral Sclerosis.
°AD: Alzheime Disease.
''MS: Multiple Sclerosis.
¨EAE: Experimental autoimmune encephalitis.
$NLRs; Nucleotide-binding oligomerization domain-like receptors.
%RAGE: Receptor for advanced glycation end products.
¢SLE: Systemic lupus erythematosus.
°°ABGA: Anti basal ganglia antibodies.
¥PANDAS: Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.
£SC: Sydenham's Chorea.
€TS: Tourette syndrome.
ÆaPL: Antiphospholipid antibodies.
¶APS: Antiphospholipid syndrome.
⌘anti-MOG: autoantibodies against the tetrameric myelin oligodendrocyte glycoprotein (MOG).
~ADEM: Acute disseminated encephalomyelitis.
⊠GBS: Guillan-Barré syndrome.

identified by a diagnostic criteria proposed by Swedo et al. which include: obsessive compulsive disorder (OCD) or a tic disorder with abrupt onset at pre-pubertal or pediatric ages, following an episodic course, associated with streptococcal infections and with neurological abnormalities (choreiform movements and motor hyperactivity).[23]

It was suspected then that the choreiform movements in SC result from localization of the anti-streptococcal antibodies in the basal ganglia, which later redefined PANDAS as an immune mediated neurological disease involving the basal ganglia.[24] A study examining 50 children with behavioral alterations, associated with tics and choreiform, found elevated titers of anti-streptococcal antibodies associated with high levels of anti-neural antibodies in children with movement disorders[25]

The inflammatory basis in SC and PANDAS seems to be linked to the activation of acuired immunity, by the production of specific antibodies, some of them as result of cross reaction between group A β-hemolytic streptococcus and neuronal tissue (as the mammalian lysoganglioside and *N*-acetyl-β-D-glucosamine (GlcNAc), an epitope in group A streptococci, which reacts with antineural antibodies, resulting in a cross-reaction between epitopes[26] others directed against basal ganglia (anti-basal ganglia antibodies- ABGA).[27] It has been hypothesized and antigenic mimicry between antibodies against epitopes in caudate nucleus and M protein in group A streptococci. In regards, an *in vivo* study reported that mammalian lysoganglioside and *N*-acetyl-β-D-glucosamine (GlcNAc), an epitope in group-A-streptococci, reacts with these antineural antibodies and this pathogenic mechanism has been confirmed by various clinical studies lead in children affected by movement disorders.[26]

In regards, Church A. et al. compared 40 children with movement disorders (fulfilling criteria for PANDAS and SC) related to group A-streptococcal infection (GAS) with controls (including one hundred neurological pediatric patients, among whom 40 children with uncomplicated streptococcal infection and 50 patients with autoimmune disorders). ABGA was present in 94% of PANDAS patients and 95% of SC patients compared to the 5% in the control group.[27] Comparison of serum ABGA of 22 PANDAS patients with the same number of controls (including patients with uncomplicated GAS infection) resulted in positive anti-basal ganglia staining (by indirect tissue immunofluorescence) in 64% of PANDAS patients versus 9% of control group, concluding that ABGAs are not present following all GAS infections.[28] On the contrary, other studies did not support a relationship between PANDAS and SC and GAS infection.[29,30]

Group A β-hemolytic streptococcus antibodies have been found positive not only in Sydenham's chorea and PANDAS, but also in Tourette Syndrome (TS), suggesting a common inflammatory patterns for all the 3 pathologies. In fact, since obsessive-compulsive behaviors (including Tics and/or obsessive-compulsive disorder (OCD)) were common in children with SC and PANDAS, it has been suggested that these types of behaviors might have a neurobiological etiopathology in the same region: the basal ganglia. Studies in children affected by OCD showed a higher level of presence of ABGA in the cerebrospinal fluid (CSF) compared to healthy children.[11] Assessment of 50 patients with a history of rheumatic fever (30 patients with SC and 20 patients without chorea), in a 6-month prospective study, showed that obsessive-compulsive symptoms appeared suddenly in 70% of patients with chorea, being absent in those without movement disorders.[31] A further study evaluated the presence of ABGA through enzyme-linked immunosorbent assay (ELISA) and western immunoblotting in 50 patients (OCD children) compared to 3 control groups (pediatric autoimmune, neurological and streptococcal controls), resulting in a 42% positive antibody binding in the cases compared to 4% in the control groups.[32]

The role of innate immunity and cytokines was also studied in the obsessive compulsive disorder (OCD) associated with SC, PANDAS and TS. A prospective longitudinal study of the levels of 10 cytokines in 46 TS patients with or without obsessive-compulsive disorders associated with SC, PANDAS and TS, reported elevated amounts of interleukin-12 (IL-12) and tumor necrosis factor α (TNF α) at baseline and during exacerbations of the disease.[33] A further study on the evaluation of 32 children and adolescents with TS, of which 17 had comorbid OCD, and 16 healthy controls, showed elevated levels of IL-12 and IL-2 in the TS+OCD group.[34] Later, an elevated expression of monocyte chemotactic factor-1 (MCP-1), interleukin-2 (IL-2) and protein tyrosine phosphatase receptor-N (PTPR-N) genes has also been reported in TS patients affected by OCD.[35] Another study in 40 TS patients and 40 healthy subjects, showed higher levels of IL-1β, IL-16, IL-17 and soluble gp130 in the former group, also showing a higher percentage of patients with positive anti-neural antibodies and anti-streptolysin titer.[36] A cross-sectional study in 4six children, adolescents and adult patients with TS and 4three healthy subjects showed decreased (but within normal range) monocyte activation state and decreased TNFα and IL-1 receptor antagonist levels in patients with TS disorder, as a consequence of possible innate immunity imbalance.[37]

Based on the pathophysiology of this disorder spectrum, treatment options seems to be directed toward 4 different goals: treatment of streptococcal infection and antibiotic prophylaxis, symptomatic treatment of movement disorders, symptomatic treatment of neuropsychiatric alterations and treatment the background inflammation.

Immunotherapeutic approaches in SC

Current therapeutic strategies focus on immunomodulation to treat the illness and antibiotic prophylaxis to prevent exacerbating infections. Among immunotherapeutic strategies, steroids have been widely studied in these patients groups, evaluating their profile both on efficacy and safety in pediatric patients.

A randomized double blind placebo controlled trial in 22 SC patients and 15 controls, showed significant reduction in clinical symptoms in the prednisone-treated group (2mg/kg for 4 weeks and tapered) in addition to a significantly shorter remission time and earlier recovery.[38] Another retrospective study, reported decreased duration of chorea in rheumatic fever patients, with prednisone treatment at standard doses compared to no treatment (4 vs. Nine weeks, respectively).[39] Later, a 4-year follow-up of on 10 patients with severe paralytic form of refractory SC (no response to conventional symptomatic therapies) treated

with intravenous methylprednisolone and oral deflazacort, showed a significant improvement in pathologic children. They had been bedridden at the start point, showed partial recovery in chewing and swallowing after 3 d and had a complete remission after 3–4 weeks. During the 4-year follow-up, none of them developed any neuropsychiatric or movement disorder.[40] Immunoglobulins have also been proposed as therapeutic strategy for SC children. Randomized trials on SC patients on the comparison between the effectiveness of intravenous immunoglobulin (IVIG) vs. plasma exchange and prednisone showed a better improvement of symptoms in the IVIG/plasma exchange group compared to the prednisone-treated group, with 72% decreased chorea severity score in the IVIG group, 50% decrease in the plasma exchange group and 29% in the prednisone group after one month (48% improvement in total; not blinded).[41] Based on this trial, a double case report of 2 severely disabled SC patients-one was wheelchair bound and had behavioral changes while the other one had severe ataxia and tics- treated with IVIG 400 mg/kg per day for 5 days, reported disappearance of symptoms in one week with no relapse in 2 y.[42] Another randomized controlled study in SC patients, compared the use of IVIG 2g/kg over 2 d in addition to the standard treatment with the standard therapy alone (oral Penicillin V K 500mg every 12 hours or 250mg every 6 hours for 10 days; Intramuscular penicillin to be given at discharge: 1.2 million units if over 30 kg and 600,000 units if weight less than 30 kg; haloperidol 0,025 mg/kg/day orally in divided doses gradually increasing to a maximum of 0,05mg/kg/day). Ten patients aged 4 to 16 with moderate to severe SC were randomized in these two groups. Clinical rating scale, brain single-photon emission computed tomography (SPECT), and the duration of symptomatic treatment showed superior results in the IVIG-treated group.[43] As far as plasma exchange treatment in this group of patients, its efficacy has not been determined yet because to our knowledge there is only one class III study, a non-blinded randomized trial, with inadequate power and insufficient evidence for the use of plasma exchange in SC.[44]

Immunotheraputic approaches in PANDAS

Apart from antibiotic therapy, research literature data have recently shown the efficacy of IVIG in this group of patients, even if the most of studies come from adult patients' trials. The only study in PANDAS children, comparing the efficacy of IVIG versus plasma-exchange (PE) date from 1999 when Perlmutter SJ et al. leaded a randomized clinical trial in 30 patients with severe exacerbations of tic disorders or OCD, comparing the use of PE (5 single volume exchanges for 2 weeks) and IVIG (1 g/kg daily for 2 days) with placebo (saline solution). Severity of OCD, depression, anxiety, tics and global function were assessed at baseline, one month and 12 months later. Nine patients were treated with IVIG, 10 with PE and 10 patients received placebo. PE-treated patients had 58% improvement in OCD scores, 47% improvement in anxiety, 49% improvement in tic symptoms in addition to 35% improvement in overall functioning. Seven of the 10 patients in plasma exchange group and 7 out of the 9 in IVIG group, (82% of patients) had no recurrence of symptoms when assessed at 12th month. IVIG-treated patients had 45% improvement in OCD symptoms, 31% in anxiety and 33% in overall functioning.[45] To our knowledge, this was the only class III study that has ever been performed in these patients and IVIG and PE to treat tics/OCD in PANDAS remains investigational.

It should be mentioned that an open label study in 5 patients with untreated OCD without exacerbation by streptococcal infections (not PANDAS), showed no improvement in their symptoms when treated with PE.[46]

Immunotherapeutic approaches in TS

As in SC and PANDAS, PE and IVIG have been proposed as therapeutic strategies in TS. In regards, a case study of 4 children with sudden-onset moderate to severe TS and OCD (One with TS, one with OCD and 2 affected by both) reported that the use of PE (in 2 patients), IVIG (in one subject) and prednisone (in one child) resulted in immediate improvement.[47] In another case report, PE was used for treating acute worsening obsessive compulsive symptoms in an adolescent boy after GAS infection and resulted in dramatic reduction in the size of his basal ganglia, previously enlarged in the course of his symptoms.[48] Antibodies to caudate nucleus, using Western blotting, in a study of 60 children with tics and TS, were detected in 10 patients. Seven patients with refractory TS (no response to neuroleptics). These children received intravenous immunoglobulins with gradual improvement in behavior and tics, going to remission for over 6 months.[49] However, a double-blind randomized controlled trial study of 30 adult patients with tic disorder did not report statistically significant difference between IVIG (1 g/kg in 2 days) and placebo.[50] As far as biologic drugs are concerned, the use of celecoxib was beneficial in one pediatric case with chronic TS.[51]

Immunotherapeutic approaches of chorea as manifestation of other pediatric autoimmune diseases

Movement disorders can present as manifestation of systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) in children, however when present, chorea is the most common movement disorder in these patients.[52] Three mechanisms have been proposed for development of chorea in SLE: vasculopathies (hypoxic ischemic damage to basal ganglia), immune complex deposits and infections. Antiphospholipid antibodies (aPL) have been related to chorea pathogenesis, although the pathophysiologic mechanism is not fully elucidated. It seems that aPL can bind to endothelial cells and disrupt the blood-brain-barrier and consequently can also bind to neuronal cell surface, exerting a neurotoxic action.[53] Movement disorders in SLE and APS have been studied by Lazurova I et al. who reported 6 cases of SLE and APS associated with movement disorders, with 4 patients affected by generalized chorea as first manifestation of the disease, 2 of them affected by SLE with positive aPL and the other 2 only with positive aPL. The four of them were treated with methylprednisolone followed by oral prednisone. The remaining 2 patients were affected by SLE associated with Parkinsonism movements and 2 had an exacerbating course (unresponsive to methylprednisolone and cyclophosphamide therapy),

until plasma exchange or rituximab were used. This study also showed that all of these 6 children had increased IgG neuronal cell-surface bindings (neuronal cell lines with dopaminergic activities) when compared to controls (12 healthy individuals and 13 children with other neurological diseases). Therefore, the authors concluded that immune-suppressive therapies rather than anticoagulative therapies should be considered in movement disorders associated with SLE and APS.[54] Combined use of immunosuppressive agents and glucocorticoid therapy has also been suggested for a better control of SLE with neuropsychiatric manifestations (including aPL-associated chorea), in addition to conventional symptomatic therapies.[55] Use of IVIG in SLE-associated chorea has been mostly studied in adult patients, with successful treatment of the movement disorders. To our knowledge, only one study in pediatric age has evaluated their efficacy in SLE-associated movement disorders. The authors evaluated 2 children with aPL-associated chorea triggered by streptococcal and varicella infection. Haloperidol, valproic acid and oral prednisone failed to treat those patients, however, one month after 2 courses of IVIG treatment, symptoms were completely resolved.[56]

Inflammatory demyelinating diseases in pediatrics

Inflammatory demyelinating diseases are conventionally divided to two groups in pediatric age: those affecting the central nervous system (CNS) and those affecting the peripheral nervous system (PNS). They are also categorized based on their etiology: infectious, autoimmune and hereditary. The autoimmune category, also known as idiopathic inflammatory demyelinating disease (IIDD) includes diseases such as acute disseminated encephalomyelitis (ADEM), site-restricted acute inflammatory demyelinating diseases (such as transverse myelitis, cerebritis, optic neuritis), multiple sclerosis (MS), neuromyelitis optica (Devic's disease), all of which involve the CNS within a broad range from unifocal to multifocal lesions. Guillain Barre syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are the examples of those involving the PNS.[57]

The immunopathophysiology of ADEM and therapeutic interventions

Acute disseminated encephalomyelitis (ADEM) is a self-limiting monophasic multifocal inflammatory CNS disease, involving the white matter of the brain and the spinal cord that occurs either after vaccination and certain kind of infections. Other than monophasic course, ADEM can also have a recurrent course (development of similar symptoms to the first episode without new MRI lesions) and a multiphasic course (Involved regions and symptoms are different from the first episode). Relapses occur in 25% of patients, following either the recurrent or multiphasic course. This further emphasizes the importance of distinguishing between ADEM and MS.[58] The exact etiology of ADEM seems to be unknown, however infectious-triggered autoimmune mechanisms have been postulated. Also the detection of autoantibodies against the tetrameric myelin oligodendrocyte glycoprotein (MOG) further highlights the involvement of inflammation in pathogenesis of ADEM. Based on the similarity between ADEM and experimental allergic encephalomyelitis (EAE), cross reactivity of myelin proteins and microbial structures, innate immunity dysregulation, auto-reactive T cells and destruction of oligodendrocytes may be considered to be responsible in ADEM. In particular, translation of studies of animal models of EAE to human ADEM indicates that mechanisms such as molecular mimicry or direct CNS infection with secondary inflammatory cascade may play leading roles in ADEM pathogenesis. These processes may result in tissue damage with leaking of auto-antigens into the systemic circulation where they are processed by peripheral immune mechanisms, leading to a self-directed autoimmune attack against the CNS driven by encephalitogenic T cells. The molecular mimicry hypothesis suggests that structural similarities between the pathogen and the host are sufficient to induce T-cell activation but not sufficient to induce tolerance. Activated T cells (and secondarily activated B cells) may then reactivate when encountering local antigen presenting cells while patrolling the CNS.[59] ADEM associated with vaccines may be related to contamination with myelin antigens from CNS culture tissue. Recent data suggest that Th1 and Th2-related chemokines are produced in ADEM and MS but that relatively selective up-regulation of chemokines active on neutrophils and Th2 cells may occur in ADEM.[60] Although ADEM is usually a rare self-limiting disorder, relapses might also occur and the recovery might be incomplete in those left untreated. The disease is rare and necessitates urgent interventions; as a result, no controlled trial has been performed in children. No standard treatment has actually been established for ADEM and it is mostly treated with nonspecific immunosuppressive methods such as corticosteroids, IVIG and PE.[61]

Intravenous methylprednisolone seems to be the current first line of treatment in childhood ADEM, but has been used in different regimen. The most commonly used regimen is 10–30 mg/kg/day (Maximum dosage: 1g/day) of intravenous methylprednisolone for 3–5 days, followed by oral prednisone for 4–6 weeks. Tapering methylprednisolone in less than 3 weeks has been associated with relapses.[62] It has been reported that 50% to 80% of patients have fully recovered following this treatment.[63]

Studies on the use of IVIG in pediatric ADEM have emphasized their role in the treatment of the disease. An observational case study reported 3 children, aged 2 to 5 years, affected by ADEM, successfully treated with high dose IVIG (400 mg/Kg/day) in 5 consecutive days, with an improvement of their consciousness in 14 hours, 2 d and 4 d respectively.[64] Another observational study on 4 pediatric patients affected by corticosteroid-resistant ADEM (with no improvement after receiving a 3–5 day course of high dose intravenous methylprednisolone) showed rapid improvement after administration of IVIG.[65] On a review of 20 pediatric cases of monophasic ADEM, 70% have shown complete recovery after IVIG or IVIG plus steroids. In the 5 case reports with recurrent ADEM, 2 were completely recovered after IVIG.[66] Imitaka G et al. have recently reported a case of successful treatment of steroid-resistant ADEM in a 10-month-old infant with 5 d of 400 mg/kg/day of IVIG, which resulted in complete recovery of the infant.[67] A maintenance therapy of monthly IVIG is also reported in 2 case reports.[68,69]

As a result, the use of IVIG has been recommended in treatment of monophasic ADEM as the second-line treatment, when corticosteroids seem to be contraindicated and for preventing steroid dependency. In ADEM plasmapheresis (plasma exchange-PE) or IVIG is considered for those patients who do not respond to glucocorticoid therapy. The most literature data on the use of PE in ADEM comes from adult cases. PE was first successfully used in treatment of 2 steroid-resistance fulminant ADEM cases.[70]

A randomized cross-over controlled trial of steroid-resistant adult ADEM patients treated with PE, reported moderate improvement in neurological disability during 42.1% of PE courses compared to 5.9% of courses of sham treatment. Three patients from the sham group improved after crossover to PE group. On the contrary, those who failed the PE group did not improve after crossover.[71,72] A review of 49 adult patients with severe attacks of CNS demyelination (22 with MS, 10 affected by ADEM and 10 by neuromyelitis optica) indicated that moderate to marked functional improvement was seen in 44.1% of patients treated with 4 to 6 courses of PE. Researchers also reported that being male, preserved reflexes during the attack and early initiation of treatment with an average of 7 courses of PE, were the main determinants of improvement.[73] Another retrospective review of records of 41 adult patients with acute attacks of CNS demyelination treated with plasma exchange, indicated that early initiation of PE was significantly associated with improvement in 6 months. In the same study, use of PE resulted in recovery of 63% of patients. Those patients who had not recovered early by PE (12 patients, 48%) did not get any better at follow-up.[74] A further retrospective review of 35 adult patients, concluded that 77% of steroid-resistant patients were improved after treatment with PE.[75] Successful use of PE was also described in some case reports including pediatric cases as well.[76-79] Moreover, a retrospective analysis of acute demyelinating disorders in children (10 steroid-resistant patients with acute relapses of multiple sclerosis, neuromyelitis optica and ADEM) evaluated the efficacy of PE. It was reported that Expanded Disability Status Scale (EDSS) improved within one month. Three patients (3 of 7 affected eyes) had worsened visual acuity that was improved at follow-up.[80] Immunosuppressant therapy has been suggested in those cases when IVIG and plasma exchange had failed and cyclophosphamide has been used as the third-line treatment in fulminant ADEM in an adult patient.[81]

Pediatric Multiple Sclerosis (MS), immunopathogenesis and therapeutic interventions

Immunopathogenic hypothesis in MS

While ADEM presents as a monophasic benign CNS demyelinating disease, multiple sclerosis (MS) is a chronic demyelinating multifocal disease with variable course and is an important differential diagnosis in this category. It has been reported that an average of 20% (1545%–) of patients with multiple attacks who have been initially diagnosed with ADEM, actually have MS.[82] Although MS usually occurs between 20 and 40 y of age, a small number of patients develop their symptoms during childhood or adolescence. It has been reported that about 2 to 10% (5% on average) of MS patients show symptoms before the age of 18 and approximately 1% show symptoms before the age of 10.[83] The female predominance is slightly different from that of adult MS; in patients older than 10 years, female to male ratio is 2.1–3:1 and in younger patients it is 0.8–1.6:1. Most patients follow a course of relapsing remitting disease similar to adults.[84]

Pediatric MS is defined based on the 2010 McDonald criteria: 2 typical MS attacks, affecting the brain, spinal cord and optic nerve with one month interval; a first clinical event with involvement of at least 2 of MS- specific sites in MRI (periventricular, juxtacortical, infratentorial, or spinal cord) and dissemination in time (clinically-silent enhancing or non-enhancing on T1-weighted images); one attack of ADEM followed by a second none-ADEM event after 3 months; one typical MS event (without encephalopathy) and MRI demonstrating at least one new T2 lesion on a scan more than 30 d after the attack.[85] The first attack of MS is also known as clinically isolated syndrome (CIS). MRI is used for diagnosis of MS and is considered positive when 3 of these 4 criteria are positive: $\geq$9 white matter lesions, $\geq$3 periventricular lesions, 1 juxtacortical lesion and one infratentorial lesion. Also two MRI lesions with abnormal CSF (oligoclonal band or elevated IgG) are consistent with MS diagnosis.

As far as MS immunopathogenesis is concerned, although active MS lesions seem to be characterized by inflammation processes involving T lymphocytes and macrophages, evaluation of the earliest lesions from biopsy or autopsy material has shown significant pathological heterogeneity classifiable into 4 distinct patterns. The first pattern is characterized by focal demyelinated lesions associated with T lymphocytes and macrophage infiltration. The second one shows immunoglobulin deposits and complement activation at sites of active myelin breakdown. In the third pattern, lesions are both inflammatory and ill-defined plaque borders, demonstrating myelin sparing around blood vessels. These lesions are characterized by a selective loss of myelin-associated glycoprotein (MAG), decrease of oligodendrocyte density, oligodendrocytes apoptosis, and minimal remyelination. The fourth pattern is characterized by nonapoptotic oligodendroglial death in the adjacent normal-appearing periplaque white-matter, possibly owing to metabolic or toxic factors, even if the pathogenic mechanism remains still unclear. The MS immunopathogenesis background should be based on the inflammatory nature of CNS lesions, the later development of secondary progressive disease and the lesional heterogeneity outlined above. It has been proposed the participation of several elements of the immune response in MS, including activated helper T-cell subsets and termed Th1 and Th2 inflammatory cytokines. The initial step in development of an inflammatory MS lesion is considered to be activation of circulating autoreactive T lymphocytes by factors such as infection, superantigen stimulation, or effects of reactive metabolites or metabolic stress. These activated T lymphocytes interact with endothelial surface integrins, such as very late antigen-4 (VLA-4) to injure and breach the blood– brain barrier, with injury mediated in part through matrix metalloproteinases (MMPs), in particular, MMP-9. Upregulation of endothelial adhesion molecules [e.g. intercellular adhesion molecule-1

(ICAM-1), vascular cell adhesion molecule (VCAM-1), and E-selectin permits further ingress of pathogenic inflammatory cells. T lymphocytes recognize antigens in association with major histocompatibility complex (MHC) class II molecules and CD8. Once activated, CD4. T lymphocytes in MS appear to develop a Th1-dominant profile with up-regulation of IL-2, IFN-gamma, and TNF-α. Their cytokines activate macrophages, which play a direct role in demyelination. Other factors contributing to myelin and axonal injury may include production of demyelinating antibodies, direct toxicity of pro-inflammatory cytokines, chemokines, and other soluble mediators, cytotoxic CD8. T-lymphocyte/ MHC class I-mediated injury, production of reactive oxygen and nitrogen species, excitotoxic glutaminergic mechanisms, or oligodendrocyte injury.[86] Nevertheless, if on one hand the T-cell involvement in the immunopathogenesis of MS has been established, on the other hand there is increasing interest in underlying the role of humoral immunity in MS. In regards it has been demonstrated the presence of dominant B-cell clonotypes in CSF and MS lesions, suggesting an antigen-driven selection process.[87]

Pediatric MS immunotherapeutic approaches

Literature guidelines report that the first-line treatment for acute MS is intravenous methylprednisolone (20–30 mg/kg, max: 1g for 3 to 5 d followed by oral prednisolone, gradually tapered over 2–3 weeks), while second line treatment consists in the administration of IVIG (1 g/kg per month or every 3 months for 6 to 12 months, with or without initial 400 mg/g/day for 5 days) or plasma exchange.[88] Nevertheless, to our knowledge no randomized controlled trial has compared the efficacy of these drugs in pediatric group so far.[89] Although no specific treatment protocol is defined in childhood, IVIG is not recommended for routine use of pediatric MS and is reserved for those patients with severe refractory optic neuritis. The use of PE for pediatric MS is also confined to patients with a small gap between acute MS attacks. Similar to adult MS, disease modifying therapy (DMT) should be considered in pediatric MS as well. Not been officially approved for children, the first line of DMT is interferon β (1a and 1b) (IFNβ) and glatiramer acetate (GA).

Interferon β can cause alterations in cytokine production and T-cell proliferation. The two therapeutic forms are IFNβ1-a (2 available types; one is administered intramuscularly once per week and one is administered subcutaneously 3 times per week) and 1-b (subcutaneous injection every other day). Elevated liver enzymes, flu-like symptoms and injection site reactions are the most common adverse effects of these therapies. Glatiramer acetate (GA) is a polypeptide that mimics the myelin basic protein (MBP), thereby effecting T-cell functions. GA is administered subcutaneously every day and the most common adverse effects is injection site reactions. Open-label studies have supported the safety and efficacy of these drugs.[90] The results of a retrospective longitudinal open label study of 258 MS patients with pediatric onset, indicated that IFNβ and GA were the most common prescribed drugs. IFNβ was prescribed to 200 (77.5%) and GA was prescribed to 53 (20.5%) patients as the first line treatment. Among them, 144 (55.8%) were successfully treated with the first line drugs; 65 (25.2%) proceeded to the second drug, 29 (11.2%) and 20 (7.8%) received 3, 4, or more sequential therapies respectively. It has to be mentioned that 78.7% of patients had used IFNβ and GA as second therapeutic agent and 21.3% had used other DMTs.[91] According to the International Pediatric Multiple Sclerosis Study Group (IPMSSG), all pediatric MS patients should receive either IFNβ or GA. Due to the reduction in frequency of relapses and neuroimaging evidences of reduced disease activity, plus studies that support the efficacy and safety of these drugs, they are used as first-line treatment in pediatric MS as well as adult patients, while not officially approved for use in children.[82] There are limited controlled studies and sparse data on the appropriate dosage in children.[92] For those children who do not respond to the first-line treatment with immunomudulatory drugs mentioned above and for those with severe frequent attacks progressing rapidly to disabilities, immunosuppressive drugs are used as second line of treatment. Since children are a sensitive population, effects of these long-term prescribed drugs such as immune system development and effects on fertility and puberty, mandates that all children with diagnosis of pediatric MS be included in clinical trials of pediatric MS and monitored precisely.[89]

Azathioprine (1–2 mg/kg/day or lower) is commonly used as the second line treatment of pediatric MS. However it is not approved in the US and most European countries. Hematological abnormalities, abnormal liver function tests and gastrointestinal problems have been reported as adverse effects of this drug and a small preponderance to secondary cancer development is also suspected.[89] Methotrexate is the other rarely used drug in pediatric MS. Mitoxantrone has shown efficacy in adult MS patients, however cardiotoxicity, liver toxicity, myelosuppression and increased risk of leukemia have been reported as adverse effects and restricted its use.[93] In children, a retrospective study of 4 pediatric MS patients with frequent disabling relapses, with a follow-up of 3.8 to 18 years, showed that the severities and frequencies of relapses had decreased after one year of treatment with mitoxantrone. Researchers did not observe any long-term adverse effect.[94] Another study of 19 pediatric MS patients treated with mitoxantrone with a median follow-up period of 30 months, reported that 14 cases (73%) had no relapses in their follow-up period. The volume of the gadolinium enhancing lesion in MRI of these patients had decreased in 16 cases and the EDSS score had also decreased in 16 patients. The study also reported transient and mild adverse effects such as alopecia, cardiomyopathy and leukopenia.[95] Cyclophosphamide is usually suggested for secondary progressive MS and for younger adult MS patients (≤40 years). The retrospective study of 17 children reported reduction in relapse rates and stabilized EDSS after one year of treatment with cyclophosphamide. Of this studied group, 14 patients had received IFNβ or GA, 9 had received more than one DMT and 2 had been treated with mitoxantrone previously. These patients received cyclophosphamide either as induction therapy (2 patients), monthly administration (7 patients) or induction therapy followed by monthly administration(8 patients). Three children became relapse-free and 12 children had reduced rates of relapses (from 3.8 per year

to 1.6) Gastrointestinal problems, lymphopenia, anemia, alopecia were among the more frequent adverse effects. Also, 3 patients developed amenorrhea, one became infertile, 2 developed osteoporosis and one patients got transitional cell carcinoma of the bladder.[96]

In recent years, Natalizumab, a humanized monoclonal antibody, is approved for treatment of relapsing remitting MS in adult patients with a dosage of 300 mg monthly infusion and its efficacy has been supported by randomized controlled trials in adult MS, reducing relapse rates (68% reduction), disease progression (slowing it by 54%) and development of new lesions.[89] The use of natalizumab in pediatric patients has recently been evaluated. In regards, a case report study on 3 patients (previously treated with IFNβ or GA, still experiencing relapses) receiving a dosage of 300 to 500 mg/kg, every month for 2 years, resulted in significant improvement of their symptoms. No relapses, no significant adverse effect and no new MRI lesions were detected in these patients.[97] Another case report, described a patients with frequent relapses despite treatment with IFNβ for 10.5 month, who received 300 mg/kg natalizumab and showed complete response and suppression of the disease activity in her MRI studies.[98] A prospective study of 19 pediatric patients treated with natalizumab (300 mg/kg every 4 weeks) reported significant decrease in disease activity.[99] Later, a study of 24 pediatric-adolescent patients with refractory MS in 75% of them received natalizumab as fourth or fifth therapeutic agent, 20 patients (83%) showed favorable response in both clinical and MRI criteria. Natalizumab was ceased in 4 patients due to hypersensitivity reactions and poor tolerance.[100,101] The safety and efficacy of natalizumab in pediatric patients is going to be further evaluated in an ongoing study (ID: NCT02137109). The most important adverse effect of natalizumab in adult MS patients is progressive multifocal leukoencephalopathy (PML), a rare and fatal CNS infection caused by JC virus. Estimated risk of PML in those who receive natalizumab for 25 to 48 months is 11.1 per 1000 individuals.[102] To our knowledge, no natalizumab-related PML cases has ever been reported in pediatric MS patients. May be children on immunosuppressive agents have lower risks of PML.[100] Although it seems that natalizumab is well tolerated and effective in children, further studies on the long-term effects of this drug in this population are mandatory.

Finally, some newer drugs are also considered for further use in pediatric MS including rituximab, fingulimod, cladribine, teriflunomide, laquinimod, fumarate, daclizumab and alentuzumab. However data on efficacy and safety are still insufficient for a conclusion.

Immunotherapy in other demyelinating CNS diseases

Among demyelinating diseases, we can mention the Schilder's disease or myelinoclastic diffuse sclerosis, often considered as a MS variant. Children 5 to 15 y are affected by this disease, with equal gender involvement and no prior vaccination or infection has ever been established as possible cause. Large bilateral lesions in the centrum semiovale and parieto-occipital white matter appear in imaging studies. Patients develop neuropsychiatric symptoms such as behavioral disturbances and dementia, in addition to severe neurological symptoms such as ataxia, hemiplegia, blindness, muscle weakness, hemiplegia and aphasia. CNS analysis is usually normal in this disease and its progression is usually more severe than MS, however it can also appear as a monophasic or remitting demyelination and be fatal. According to case reports, similar to MS, corticosteroids, immunoglobulins, azathioprine and cyclophosphamide are used for treatment of these patients.[103]

Devic's neuromyelitis optica (NMO) is the other disease of interest in this category that involves the spinal cord and optic nerve. Antibodies against aquaporin-4 located in astrocytes foot processes are responsible for the symptoms such as complete loss of vision and pain in the eye movement as well as transverse myelitis symptoms such as paraparesis and incontinence. The course and severity are variable ranging from monophasic to multiphasic. The disease usually affects young women, with a mean age of 29, but has also been reported in children.[104] There is no definite therapy in pediatric NMO. There have been only isolated case reports with favorable results. Methyl prednisolone, IVIG and plasma exchange followed by weekly rituximab have been successfully used for challenging cases.[105,106] A retrospective observational study reviewed 5 pediatric NMO patients, who were treated with methylprednisolone and oral prednisone, followed by plasma exchange or IVIG but had no clinical improvements. Rituximab was effective and symptoms either stabilized or improved after treatment.[107] Azathioprine, cyclophosphamide, mitoxantrone and mycophenolate mofetil have also been used in some cases.[108] Interferon has not been as effective as other immunosuppressive drugs and is not recommended.[109] Overall little data of definite treatment is available due to the rarity of the disease.

Guillain Barre Syndrome: immunopathogenic basis and rationalized therapeutic approaches

Guillain Barre Syndrome (GBS) is a rare acute demyelinating disease involving the PNS. Progressive symmetrical weakness starting from lower extremities with decreased reflexes is the hallmark of this disease. The muscle weakness can progress to respiratory muscles and patients might need mechanical ventilation and intensive care. Autonomic dysfunctions like cardiac arrhythmias and blood pressure instability also occur in 2 thirds of cases. The disease reaches its peak in 2 weeks (starting from 12 hours to 28 days) and then reaches a plateau. It usually has a monophasic course but recurrent attack have also been reported in 7% of cases. Majority of patients recover in one to 2 months, however, motor deficits might persist in 10% to 20% of patients. A one-year mortality of 4% to 15% has been reported. The incidence is estimated to be 0.5–1.5 per 100,000 people 18 y and younger. Boys are affected 1.5 times more than girls.[110] Different subtypes have been described for GBS and the most common of which is the acute inflammatory demyelinating polyradiculoneuropathy (AIDP). Other important subtypes are the acute motor axonal neuropathy (AMAN), the acute motor and the sensory axonal neuropathy (AMSAN) and the Miller–Fisher syndrome (MFS) (regional variant). Infections such as *campylobacter jejuni* and vaccinations are known as the triggering factors. The trigger point of the disease is known to be the antigenic mimicry of lipooligosaccharides of the bacterial wall to gangliosides. The pathological theory is based on autoantibodies to myelin, complement

Table 2. Resume of the immunotherapeutic approaches used for the treatment of the most frequent pediatric neurodegenerative disorders

Type of movement disorder	Study Design	Number of patients	Drugs and dosages	Efficient/not efficient	Author, years of study, reference number
SC	Randomized clinical trial (RCT)	22 patients, 15 controls	Methylprednisolone 2 mg/kg, 4 weeks	Efficient	Paz et al, 2005, (72)
SC	Retrospective, observational	584 cases of rheumatoid fever, 177 SC patients, 32 prednisone-treated patients vs 14 untreated	Methylprednisolone	Efficient	Walker et al, 2007, (73)
SC	Prospective, observational	10 patients with severe paralytic SC	Methylprednisolone tapered with oral Deflazocort	Efficient	Fusco et al, 2012, (74)
SC	RCT	18 patients	4 patients IVIG, 6 patients methylprednisolone, 8 PE	IVIG more efficient than PE, more efficient than methylprednisolone	Garvey et al, 2005, (75)
SC	Case report	2 patients	IVIG 0.4 mg/kg/day for 5 days	Efficient	Van Immerzeel, 2010, (76)
SC	RCT	10 patients, 10 controls	IVIG 2 g/kg, vs standard treatment	Efficient	Walker et al, 2012, (77)
PANDAS	RCT	30 patients	10 patients PE 5 exchanges for 2 weeks, 9 patients IVIG 1g/kg for 2 days, 10 patients placebo saline solution	PE more effiecient than IVIG than placebo.	Perlmutter et al, 1999, (79)
TS	Case study	1 TS, 1 OCD, 2 both	IVIG in one patients, prednisolone in 1 and PE in one	Efficient	Allen et al, 1995, (81)
TS	Prospective, Observational	7 patients with neuroleptic resistant TS among 60 TS patients	IVIG 1 g/kg	Efficient	Zykov et al, 2009, (83)
TS	Case report	1 patient	Celecoxib	Efficient	Muller, 2004, (85)
ADEM	Case report	3 patients	IVIG 400 mg/kg/day for 5 days	Efficient	Nishikawa et al, 1999, (111)
ADEM	Observational	4 steroid-resistant patients	IVIG 400 mg/kg/day for 5 days	Efficient	Pradhan et al, 1999, (112)
ADEM	Case report	1 steroid refractory patient	IVIG 400 mg/kg/day for 5 days	Efficient	Hahn et al, 1996, (115)
ADEM	Case report	1 steroid refractory patient	IVIG 400 mg/kg/day for 5 days	Efficient	Imataka et al, 2014, (114)
ADEM	Case report	2 patients	PE	Efficient	Kanter et al, 1995, (117)
ADEM	Case report	1 patient	PE 4 times (after methylprednisolone and IVIG with no results)	Efficient	Miyazawa et al, 2001, (123)
ADEM	Retrospective, observational	13 patients	PE 5 sessions (in 12 patients who did not respond to methylprednisolone and IVIG)	Efficient	Khurana et al, 2005, (126)
MS	Retrospective, observational	4 patients	Mitoxantrone with cumulative dose of 36, 68, 84 and 120 mg/m	Efficient	Kornek et al, 2011, (164)
MS	Retrospective, observational	19 patients	Mitoxantrone 20 mg	Efficient	Etemadifar et al, 2014, (165)
MS	Retrospective, observational	17 patients	Cyclophosphamide	Efficient	Makhani et al, 2009, (166)
MS	Case report	3 patients	Natalizumab, 3–5 mg/kg every 4 weeks, after no response to IFN-βand steroid	Efficient	Huppke et al, 2008, (167)
MS	Case report	1 patient	Natalizumab, 3–5 mg/kg every 4 weeks, after no response to IFN-βand steroid	Efficient	Borriello, 2009, (168)
MS	Prospective, observational	19 patients	Natalizumab, 300 mg every 4 weeks	Efficient	Ghezzi et al, 2010, (169)
NMO	Case report	1 patient	4 courses of rituximab, 375 mg/m^2, every other week	Efficient	Dembinski et al, 2013, (192)
NMO	Retrospective, observational	5 patients	Rituximab	Efficient	Longoni et al, 2014, (193)

(*Continued*)

NMO, Devic's disease	Case report	1 patient	Mycofenolate mofetil, 2 g/day, after no response to methylprednisolone and azathioprine	Efficient	Falcini et al, 2006, (200)
GBS	RCT	18 patients; 9 cases, 9 controls	IVIG 1 g/kg/ day for 2 d and supportive treatment	Efficient	Gurses et al, 1995, (239)
GBS	Comparative study, prospective	7 patients 8 comparable children receiving PE	IVIG 0.4 g/kg/day for 5 days, PE in comparison group	Efficient	Abd-allah et al, 1997, (242)
GBS	Comparative study, prospective cases, retrospective controls	33 patients with very severe GBS; 22 cases, 11 controls	IVIG 0.4 g/kg/day for 5 d and supportive treatment for the other group	Efficient	Singhi et al, 1999, (240)
GBS	RCT- 2 parts	21 patients in study 1 51 patients in study 2	IVIG 1 g/kg for 2 d vs no treatment in study 1 IVIG 1g/kg for 2 d vs 0.4 g/kg for 5 days	Efficient, study 2: no difference	Korinthenberg et al, 2005, (241)
GBS	RCT	20 cases received IVIG, 21 patients received PE	IVIG 0.4 g/kg/days for 5 d in cases, 5 day courses of 1 volume of PE in the second group	In children requiring mechanical ventilation (MV), PE is better than IVIG regarding the duration of MV but not PICU stay or the short term neurological outcome	El-bayoumi et al, 2011, (243)

activation and finally degeneration of axons with different severities in peripheral nerves. The immunopathogenesis of GBS is still not well clarified, also because of its different forms of presentations which subtend peculiar pathogenic aspects. Nevertheless the common feature of the GBS forms is the immunological involvement of myelin, mostly by a mechanism of antigenic mimicry, secondary to the production of antiganglioside antibodies. Therefore, demyelination is the most typical pathological feature. There is prominent lymphocytic infiltration in the peripheral nerves and macrophage invasion in the myelin sheath and Schwann cells. Cellular immunity is of critical importance.[111] Studies on GBS patients have shown that auto-reactive T-cells recognize a specific auto-antigen presented by major histocompatibility complex class II molecules and the simultaneous delivery of co-stimulatory signals on the cell surface of antigen-presenting cells, such as macrophages, in the systemic immune compartment. Activated T-lymphocytes can cross the blood-nerve barrier in order to enter the peripheral nervous system. Within the peripheral nervous system, T-cells activate macrophages that enhance phagocytic activity, production of cytokines, and the release of toxic mediators, such as nitric oxide, matrix metalloproteinases, and pro-inflammatory cytokines, propagating demyelination and secondary mild axonal loss.[94]

GBS immunotherapeutic approaches

Other than supportive and symptomatic therapy in GBS, disease modifying therapies seem to be essential dimensions of treatment. If in this occasion steroids have not, surprisingly, been demonstrated to be successful in GBS treatment.[112] PE has been shown to be efficient and safe and its use was reported since 1980s.[113-116] PE (five times in 2 weeks) has been associated with less damage to the nerves and clinical improvement and been particularly effective when started within 7 d of onset and in those who need mechanical ventilation.[117] In regards, most clinical trials have been lead on adult patients affected by GBS, while only one trial examined both adult and pediatric GBS, showing PE efficacy in the disease treatment and older age was associated with poor outcome in this study.[118]

IVIG has been considered another treatment option in GBS patients. It has to be administered in the first 2 to 4 weeks of onset of the disease and was introduced as "at least as effective as PE" in first adult studies.[119,120] Nevertheless, based on the report of the quality standards subcommittee of the American academy of neurology in 2004, PE and IVIG are considered for severe pediatric GBS patients and corticosteroids are not recommended. In children, some clinical trials have been based on the use of IVIG as GBS treatment and the first one was a randomized study of IVIG (1 g/kg per day in 2 days) in 9 pediatric GBS patients compared to 9 patients who were only given supportive care, showing that the use of IVIG is safe and helps patients recover sooner.[122] Another study on 33 children with severe GBS, admitted to Pediatric Intensive Care Unit (PICU), examined the effects of IVIG in treatment group (supportive care plus IVIG 0.4 g/kg for 5 d in 22 patients) compared to control group (11 patients who only received supportive care). Shorter recovery period, shorter stay in PICU, sooner ambulation and less need for

activation and finally degeneration of axons with different severities in peripheral nerves. The immunopathogenesis of GBS is still not well clarified, also because of its different forms of presentations which subtend peculiar pathogenic aspects. Nevertheless the common feature of the GBS forms is the immunological involvement of myelin, mostly by a mechanism of antigenic mimicry, secondary to the production of antiganglioside antibodies. Therefore, demyelination is the most typical pathological feature. There is prominent lymphocytic infiltration in the peripheral nerves and macrophage invasion in the myelin sheath and Schwann cells. Cellular immunity is of critical importance.[111] Studies on GBS patients have shown that auto-reactive T-cells recognize a specific auto-antigen presented by major histocompatibility complex class II molecules and the simultaneous delivery of co-stimulatory signals on the cell surface of antigen-presenting cells, such as macrophages, in the systemic immune compartment. Activated T-lymphocytes can cross the blood-nerve barrier in order to enter the peripheral nervous system. Within the peripheral nervous system, T-cells activate macrophages that enhance phagocytic activity, production of cytokines, and the release of toxic mediators, such as nitric oxide, matrix metalloproteinases, and pro-inflammatory cytokines, propagating demyelination and secondary mild axonal loss.[94]

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There are studies on the comparative evaluation of efficacy of IVIG vs. PE in pediatric patients affected by GBS. In regards, 7 children with GBS who were treated with IVIG (0.4 g/kg/day for 5 days) were prospectively evaluated. The results of IVIG treatment were compared with the results of a prior study in the same institution in which comparable children were treated with PE. Authors concluded that IVIG-treated children had shorter PICU stays.[125] A recent randomized study in mechanically ventilated children with GBS, compared 20 patients treated with IVIG (0.4 g/kg/day for 5 days) to 21 patients receiving plasma exchange for 5 courses. The study concluded that patients who received PE, had significantly shorter periods of mechanical ventilation. They also had shorter PICU stay but this difference was not significant. Members of both groups recovered in 4 weeks.[126] Newer therapies for GBS are in course of experimental studies and are also finding their way into clinical practice, however, there is still lack of sufficient evidences to propose them as standard treatment for this disease.[127,128]

Conclusions

Neurodegenerative disorders actually constitutes a clinical challenge for pediatrician both from a diagnostic and a therapeutic point of view, as their pathogenesis is still object of study, and immunotherapeutic approaches are not still standardized for pediatric age. While progress for adults in this therapeutic field has arisen from the development of biological drugs as targets to antigenic and immunological markers, the use of immunotherapy to treat neurodegenerative disorders has still not been standardized for children. Protocols also vary from one center to another, considering also that the most therapeutic attempts find their basis on adult studies.

This review has the purpose of collecting an extensive amount of literature data on pediatric patients affected by various neurodegenerative disorders treated by immunomodulation, representing a standardized guideline to treat these disorders in pediatric age, specifically using pediatric protocols, according to the studies collected in this paper. In regards **Table 2** summarizes all the studies above mentioned outlining all immunotherapeutic attempts, as described in literature, to treat pediatric neurodegenerative disorders.

Moreover, this review represents a starting point to evaluate what is already known and what progress will need to be made to improve the immunotherapeutic approach of treating

neurodegenerative disorders in pediatric age and to develop new pharmaceutical targets in this age group.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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