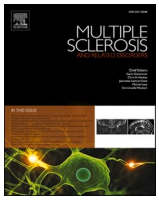
Multiple Sclerosis and Related Disorders 66 (2022) 104061

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Review article

Saudi consensus recommendations on the management of multiple sclerosis: MS management in children and adolescents

Reem F. Bunyan [a,1], Abdulaziz M. AlAbdulSalam [b,1], Rayan G. Albarakati [c], Awad A. Al Harbi [d], Dema A. Alissa [e], Ahmed H. Al-Jedai [e], Nuha M. AlKhawajah [f,g], Yaser M. Al Malik [h,i], Mousa A. Almejally [j], Hajer Y. Al-Mudaiheem [e], Hind A. AlNajashi [k], Amani A. AlShehri [l], Ibtisam A. Althubaiti [m], Rumaiza H. AlYafeai [n], Mohammed A. Babakkor [o], Edward J. Cupler [p], Mamdouh H. Ka [q], Jameelah A. Saeedi [d], Eslam Shosha [r], Mohammed A. Al Jumah [s,*]

[a] Department of Neurology, King Fahad Specialist Hospital Dammam, Eastern Region, Saudi Arabia
[b] Department of Neurology, Prince Sultan Military Medical City, Riyadh, Saudi Arabia
[c] Department of Obstetrics and Gynecology, Majmaah University, Al-Majmaah, Saudi Arabia
[d] Department of Neuroscience, King Abdullah Bin Abdulaziz University Hospital, Riyadh, Saudi Arabia
[e] Deputyship of Therapeutic Affairs, Ministry of Health, Riyadh, Saudi Arabia
[f] Department of Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia
[g] Division of Neurology, King Saud University Medical City, Riyadh, Saudi Arabia
[h] College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
[i] Division of Neurology, King Abdulaziz Medical City (National Guard Health Affairs), Riyadh, Saudi Arabia
[j] Neurology Department, Heraa General Hospital, Makkah, Saudi Arabia
[k] Department of Medicine, Division of Neurology, King Abdulaziz University, Jeddah, Saudi Arabia
[l] Pharmaceutical Care Services, King Saud Medical City, Riyadh, Saudi Arabia
[m] Department of Neurology, King Fahad Military Medical Complex Dhahran, Eastern Region, Saudi Arabia
[n] Department of Psychiatry and Psychology, My Clinic International Medical Co., Jeddah, Saudi Arabia
[o] Neurology Department, Neuroscience Center, King Abdullah Medical City, Ministry of Health, Makkah Al-Mukarramah, Saudi Arabia
[p] Department of Neurosciences, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia
[q] Department of Neurology, Al Noor Specialist Hospital, Makkah, Saudi Arabia
[r] Department of Medicine, Division of Neurology, McMaster University, Hamilton, Ontario, Canada
[s] Department of Neurology, King Fahad Medical City, Ministry of Health, Riyadh, Saudi Arabia

A B S T R A C T

Multiple sclerosis (MS) most commonly presents in young adults, although 3–5% of patients develop MS prior to the age of 18 years. The new and comprehensive consensus for the management of MS in Saudi Arabia includes recommendations for the management of MS and other CNS inflammatory demyelinating disorders in pediatric and adolescent patients. This article summarizes the key recommendations for the diagnosis and management of these disorders in young patients. Pediatric and adult populations with MS differ in their presentation and clinical course. Careful differential diagnosis is important to exclude alternative diagnoses such as acute disseminated encephalomyelitis (ADEM) or neuromyelitis optica spectrum disorders (NMOSD). The diagnosis of MS in a pediatric/adolescent patient is based on the 2017 McDonald diagnostic criteria, as in adults, once the possibility of ADEM or NMOSD has been ruled out. Few data are available from randomized trials to support the use of a specific disease-modifying therapy (DMT) in this population. Interferons and glatiramer acetate are preferred initial choices for DMTs based on observational evidence, with the requirement of a switch to a more effective DMT if breakthrough MS activity occurs.

1. Introduction

The overall prevalence of pediatric MS in Saudi pediatric patients has been estimated to be 14.33/100,000 (Bunyan et al., 20211). The presentation of MS differs between pediatric and adult patients: pediatric patients tend to present with a more inflammatory, polyfocal phenotype: more relapses, a higher frequency of cognitive impairment, more brainstem, and cerebellar involvement, higher Magnetic

* Corresponding author.
E-mail address: jumahm@gmail.com (M.A. Al Jumah).
[1] These author Contributed equally to this work.

https://doi.org/10.1016/j.msard.2022.104061
Received 30 March 2022; Received in revised form 26 June 2022; Accepted 15 July 2022
Available online 17 July 2022

Resonance Imaging (MRI) T2 burden, and less frequent appearance of CSF oligoclonal bands (Ghezzi et al., 2017; Boiko et al., 2002; Alroughani and Boyko,2018). The diagnosis and management of pediatric MS therefore presents distinct diagnostic and therapeutic challenges, compared with adult patients.

The health system in Saudi Arabia defines the pediatric age as ≤ 13 years, and adolescents as those aged 14–18 years (Bunyan et al., 2021). Here, we provide a summary of recommendations for the diagnosis and management of MS in this challenging population.

2. Methodology

An expert working group, including specialist MS neurologists, neuroradiologists, clinical pharmacists, and MS nurses (a total of 44 participating experts), representing all regions of Saudi Arabia, met on October 5, 2019. Seven groups were formed, each consisting of 6–8 experts based on their area of expertise. Seven parallel workshops were conducted, covering different topics of MS and related disorders. Each workshop was directed by an expert in a specific area. The duration of each Workshop was 3–4 h, except for the MS management workshop, which was a full-day event. Workshop facilitators identified all related internationally published guidelines for the diagnosis and management of MS. A total of 14 guidelines and consensus statements/recommendations met the criteria for use in the generation of the current consensus recommendation document. Other peer-reviewed articles with emerging evidence have also been identified and evaluated.

A consensus meeting with the nominal group technique was adopted to reach decisions on previously identified items (McMillan et al., 2016). Consensus was defined as approval of ≥ 75% of voting experts. The validity of the recommendations was not agreed on. The draft document was then compiled to include all the consensus recommendations and shared with the expert work group and MOH experts for further review and input during a 30-day feedback/comment period. The comments received were then discussed for further agreement by work group leaders in four virtual meetings held between June and July 2020, and appropriate revisions were made.

3. Diagnosis of demyelinating diseases in children and adolescents

3.1. Multiple sclerosis and clinically isolated syndrome

The diagnosis of MS in children or adolescents is similar to that in adults, and the 2017 McDonald diagnostic criteria have been validated in subjects aged < 18 years (Wong et al., 2019). Indeed, the current McDonald criteria provide substantially higher sensitivity for diagnosing MS, compared to the previous 2010 criteria. However, the McDonald criteria were unable to identify clinically definite MS in children presenting with ADEM (see below for a description of the differential diagnosis of MS and ADEM in this population) (Wong et al., 2019).

Pediatric MS may be diagnosed when 2 non-ADEM demyelinating events occur with dissemination in time and space. The International Pediatric Multiple Sclerosis Study Group (IPMSSG) has published a summary of its guidelines for diagnosing MS and other inflammatory demyelinating conditions in children and adolescents (Tardieu et al., 2016). It follows the general diagnostic approach of the McDonald criteria of demonstrating dissemination in both time and space, including a definition of pediatric MS based on a clinically isolated syndrome (CIS) following an attack of ADEM, which also demonstrates dissemination in space. However, another guideline from 2013 does not consider a CIS following an ADEM attack to be a diagnosis of MS in a young patient(8).

We recommend the use of the 2012 IPMSSG criteria for pediatric cases, given that the differential diagnosis for each disorder has been carefully evaluated and alternative diagnoses have been excluded.

Table 1
Overview of key diagnostic criteria to support a diagnosis of multiple sclerosis or other demyelinating diseases in children or adolescents.

Pediatric MS – any of the following (Tardieu et al.,2016; Rubin and Kuntz, 2013)**:** Two or more non-encephalopathic CNS clinical events separated by more than 30 days, involving more than one area of the CNS Single clinical event and MRI findings consistent with the criteria for dissemination in space (DIS), in which a follow-up MRI shows at least one new lesion consistent with dissemination in time (DIT) criteria Single ADEM episode followed > 3 months later by a non-encephalopathic clinical event with new lesions on brain MRI consistent with MS (DIS criteria) A first, single, acute event (for example, CIS) that does not meet ADEM criteria and whose MRI findings are consistent with the criteria for DIS and DIT (at least T2 lesion in at least 2 of 4 areas: spinal cord, infratentorial, juxtacortical, and periventricular [DIS], associated with simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions [DIT], if the patient is ≥ 12 years old)	**Pediatric CIS – all of the following** (Tardieu et al.,2016; Rubin and Kuntz, 2013)**:** A clinical polyfocal or monofocal CNS event with presumed inflammatory demyelinating cause Absence of a prior clinical history of CNS demyelinating disease (for example, optic neuritis (ON), transverse myelitis (TM), and hemispheric or brain-stem related syndromes) No encephalopathy (namely, no change in consciousness or behavior) that cannot be explained by fever The diagnosis of MS based on baseline MRI features (as recently defined)
Pediatric ADEM – all of the following (Tardieu et al.,2016; Rubin and Kuntz, 2013)**:** A first polyfocal, clinical CNS event with presumed inflammatory demyelinating cause Encephalopathy unexplained by fever Lack of new clinical or MRI findings at least 3 months after the onset Brain MRI is abnormal during the acute (3-month) phase. Typically, on brain MRI: Diffuse, poorly demarcated, large (> 1–2 cm) lesions involving predominantly the cerebral white matter Rare T1 hypointense lesions Deep gray matter lesions (for example, thalamus or basal ganglia) can be present	**Pediatric NMOSD – all of the following** (Wingerchuk et al., 2015)**:** Optic neuritis Acute myelitis At least 2 of the 3 supportive criteria: Contiguous spinal cord MRI lesion extending over three vertebral segments Brain MRI not meeting diagnostic criteria for MS Anti-aquaporin-4 IgG seropositive status

*MS; Multiple Sclerosis, CNS; Central Nervous System, MRI; Magnetic Resonance Imaging, CIS; Clinically Isolated Syndrome, ADEM; Acute disseminated encephalomyelitis, NMOSD; Neuromyelitis Optica Spectrum Disorder.

Table 1 provides an overview of key diagnostic criteria for MS and CIS, along with other demyelinating diseases, in the pediatric/adolescent population (Tardieu et al.,2016; Rubin and Kuntz, 2013).

3.2. Differentiating MS from other CNS inflammatory demyelinating diseases

ADEM is a polyfocal CNS disease with an underlying inflammatory demyelinating cause (Rubin and Kuntz, 2013). This condition is rare and usually occurs in children (Anilkumar et al., 2021). MS and ADEM may present similarly; however, ADEM is typically a monophasic illness. The presence of large, bilateral diffuse lesions on MRI (which are likely to have occurred over a short time period) in ADEM may differentiate this condition from the better-defined lesions disseminated in time that are diagnostic for MS (see Table 1) (Wong et al., 2019; Tardieu et al.,2016; Rubin and Kuntz, 2013; Anilkumar et al., 2021).

Additional diagnostic criteria include (Anilkumar et al., 2021).

Encephalopathy (unexplained by other causes).

- MRI lesions consistent with demyelination during the 3-month acute phase of the event
- No new clinical or MRI findings after 3 months from the acute event

Based on previous investigations and clinical workup for the diagnosis of ADEM (Tardieu et al.,2016; Pohl et al., 2016; Rostasy et al., 2016), we have reached a consensus to recommend the following:

- Gadolinium-enhanced brain and spinal cord MRI.
- CSF studies (including cell count, protein, lactate, IgG index, and oligoclonal bands).
- Screening for infectious agents, especially herpes simplex virus, enterovirus, Epstein-Barr virus, and mycoplasma.
- Laboratory studies including complete blood count, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies, NMO-IgG, MOG antibodies, liver enzymes, renal function, ESR, complement (C3, C4), ANA, dsDNA, 25-hydroxy vitamin D, ferritin, triglycerides, ACE, AQP4, and MOG antibodies, and bacterial and viral studies as indicated (blood, throat, swab, stool).

Neuromyelitis optica spectrum disorder (NMOSD) can be diagnosed according to an international consensus guideline published in 2015 (Wingerchuk et al., 2015). We agree with the published guideline and outline a brief description of a pragmatic minimum workup for diagnosis in children and adolescents below (Box 1).

4. Management of multiple sclerosis and other demyelinating diseases in children and adolescents

4.1. Multiple sclerosis

4.1.1. Disease-modifying therapies

Most disease-modifying therapies (DMTs) have not been systematically studied in children and adolescents with MS to support specific indications and dosing for use in this population (Rensel, 2019). Interferons and glatiramer acetate have been used most widely in pediatric patients with active disease requiring pharmacologic intervention, and observational data support the efficacy and acceptable safety of these agents in pediatric patients (Rensel, 2019; Ghezzi et al., 2010; Ghezzi et al., 2016; Chitnis et al., 2012).

Fingolimod was approved for pediatric MS use in Saudi Arabia, following a randomized trial in comparison with interferon beta-1a (Chitnis et al., 2018). This study found Fingolimod to be associated with fewer relapses and MRI progression as compared to interferon, but it was found to cause more serious adverse events in this study.

Pediatric patients with MS should start treatment with DMT soon after diagnosis, with regular follow-up and evaluation (Ghezzi et al., 2010).

The following recommendations are based on our consensus and expert opinion:

- Assess clinical response with regular clinical evaluations (every 3–6 months, according to label/regulatory/local guidelines) and brain MRI (every 6–12 months, according to label/regulator/local guidelines) on a patient-by-patient basis, or at the time of any relapse.
- Assess the tolerability/safety profile (every 3–6 months, based on label/regulatory/local guidelines) with periodic monitoring of blood cell count, liver function, thyroid function, and kidney function.

The recommended initial pharmacologic therapy is interferon beta (starting at 25%–50% of the adult dose, titrating to the full dose if well tolerated) or glatiramer acetate (Pohl et al., 2007). Persistent adverse tolerability findings may prompt a switch between these treatments, and persistent breakthrough MS disease activity (relapses, MRI progression, or disability progression) may warrant a switch to a different DMT. Defining an inadequate treatment response in children is complicated by their higher rate of relapse compared with adults with MS.

Inadequate treatment response to a DMT may be classified on the basis of no reduction in relapses or new T2 or contrast-enhancing MRI lesions, *or* 2 or more clinical or MRI relapses within a maximum of 12 months (Chitnis et al., 2012).

Effective and timely intervention is essential in pediatric MS, as there is preliminary observational evidence for reduced progression of cognitive impairment in pediatric MS patients treated with interferon, which requires confirmation by larger studies (Johnen et al., 2019).

Alternatively, the proposed criteria for no evidence of disease activity (NEDA) in pediatric patients include the absence of new, enlarging, or enhancing MRI lesions, relapses, or confirmed disability progression (Wong et al., 2019). Age-appropriate changes in brain volume and cognitive function may also be considered, but MS-related alterations of these parameters are difficult to define at an age when the brain is developing rapidly.

4.1.2. Relapses

The management of MS relapse in pediatric patients involves high-dose intravenous steroid pulse therapy at a dose similar to the

Box 1
Recommended minimum tests for the diagnosis of NMOSD in pediatric/adolescent patients:

The following is the recommended minimum set of diagnostic testing for children according to IPMSSG (2007) (Wingerchuk et al., 2015):

*MRI of brain and cervical and thoracic spinal cord, with or without contrast

*CSF analysis: differential cell count, total protein, IgG index, oligoclonal bands (compared with paired serum sample with isoelectric focusing and immunodetection), cytology (if possible), bacterial and viral studies as indicated, and MRZ reaction

The MRZ reaction is composed of three antibody indices against measles, rubella, and varicella zoster virus; this is positive in the majority of patients with RRMS, but is absent in other inflammatory neurological diseases.

*Complete differential blood count, erythrocyte sedimentation rate, antinuclear antibody

*CSF studies with cell count, protein, glucose, oligoclonal bands, and cytology

Given the diagnostic uncertainty that often exists in pediatric patients, a more comprehensive workup and diagnosis of pediatric MS, within the broader spectrum of acute demyelinating syndromes that may present in children, is recommended. We recommend the following investigations (in addition to brain and spine MRI) (Pohl et al., 2016):

CIS: Evoked potential (visual, somatosensory, and auditory), ophthalmology with OCT, neuropsychological testing, urology, rheumatology.

Box 2
Key elements of the management of NMOSD in children or adolescents:

*First-line therapies recommended are azathioprine (with oral steroids), rituximab, or mycophenolate mofetil (switch from azathioprine to one of the other agents in the event of suboptimal response or tolerability issues) (Chitnis et al., 2018).

*Monitor blood and liver function periodically throughout treatment.

Consider newer DMTs if poor response persists IVIg may be used as a first-line treatment when immunosuppression is contraindicated. Expert opinion provides some support for the use of IVIg for the prevention of relapse in this population at a dose of 1–2 g/day (although the optimal dose and duration of treatment are not established), especially for anti-MOG NMOSD or where the use of rituximab has resulted in hypogammaglobulinemia (Tenembaum et al., 2020).

management of ADEM (see below) (L.Banwell, 2014). Inadequate response to high-dose steroids should be treated with plasma exchange, by referring to the same evidence for this treatment in patients with fulminant disease (Lehmann et al., 2006).

4.2. Acute disseminated encephalomyelitis

High-dose corticosteroids are accepted as first-line therapy for ADEM, based on our consensus in the absence of randomized trials (Pohl and Tenembaum, 2012; Alexander and Murthy, 2011). Typically, we recommend methylprednisolone to be administered at a dose of 10–30 mg/day (maximum dose 1000 mg/day) for 3–5 days; as this is reported observationally to achieve full recovery in 50%–80% of patients. We advise a 6-week taper with oral corticosteroids to reduce the risk of relapse, but this is not strongly supported by evidence. We consider Intravenous (IV) immunoglobulin a second-line treatment in steroid-unresponsive ADEM or in combination with corticosteroids, with a total dose of 2 g/kg, administered over 2–5 days despite the lack of reliable clinical evidence for its effectiveness. Patients with fulminant disease that is refractory to therapy could benefit from plasma exchange based on a study and our expert opinion (Pohl and Tenembaum, 2012).

4.3. Acute NMO relapses

We recommend the following management for NMO relapses.

High-dose IV methylprednisolone is the standard of care recommended for the treatment of acute optic neuritis or transverse myelitis associated with NMO at a daily dose of 10–30 mg/day (to a maximum of 1000 mg daily) for 3–5 days.

Plasma exchange (PLEX) has been demonstrated to be effective in retrospective studies and case series including children with NMOSD, where high-dose steroids alone are not sufficiently effective. These studies have reported a marked improvement in visual and motor function following 5–7 cycles of PLEX.

IV immunoglobulin (IVIg) therapy has not been reliably demonstrated to be effective in the acute treatment of NMO exacerbation (Kimbrough et al., 2012). A small study reported successful relapse improvement in half of the patients with NMOSD using IVIg after a lack of response to steroids. This may warrant its further investigation as an acute therapy.

Rituximab was found to be associated with a lower risk of relapse in NMOSD patients who were seropositive for myelin oligodendrocyte or AQP4 when compared with mycophenolate mofetil (Poupart et al., 2012). However, a systematic review raised safety concerns regarding its use (Damato et al., 2016) and a recent study suggested that it may not be safe to use during the pandemic (Esmaeili et al., 2021).

Interferon beta, natalizumab, and fingolimod may be not effective and could have serious side effects on pediatric patients with NMOSD (Jacob et al., 2012; Shimizu et al., 2010).

5. Conclusion

Diagnosing pediatric MS presents a challenge given the difference in diagnostic criteria compared to adults. This is especially concerning given the deficit of practicing pediatric neurologists in Saudi Arabia which could lead to late diagnosis or predictors of worse prognosis among this vulnerable age group.

Disclaimer

Clinical practice guidelines are evidence-based decision-making tools for managing health conditions based on the highest quality of information available at the time of writing. The present recommendations are not meant to serve as fixed protocols and strict treatment guidelines that must be followed and updated regularly. They are tools to help manage MS patients that cannot replace the clinical judgment of practicing physicians. Decisions regarding treatment should be taken by the prescribing physician who should tailor the treatment regimen to the patient's medical history and individual preferences. It is recommended that physicians consult the approved product monographs within their institution's formulary for each drug for appropriate dosage, adverse effects and monitoring, and precautions for use, appropriate monitoring dosage, special warnings and precautions for use, contraindications, and monitoring of side effects and potential harm. When selecting treatment options, institutional formulary restrictions must be considered. Parts of this manuscript have been posted before on the official website of the Ministry of Health in Saudi Arabia with the consent of the authors. The posted parts have been since removed but could explain the high similarity check.

Disclosure

The authors have no conflict of interest to disclose.

Declaration of Competing Interest

Authors deny any conflict of interest.

Funding source

This consensus recommendation project was funded by the Ministry of Health, Kingdom of Saudi Arabia.

Acknowledgment

We would like to thank Editage (www.editage.com) for English language editing.

References

Anilkumar, A.C., Foris, L.A., Tadi, P., 2021. Acute disseminated encephalomyelitis. In: *StatPearls [Internet]*. StatPearls Publishing.

Boiko, A., Vorobeychik, G., Paty, D., Devonshire, V., Sadovnick, D., 2002. Early onset multiple sclerosis: a longitudinal study. Neurology 59 (7), 1006–1010.
Ghezzi, A., Baroncini, D., Zaffaroni, M., Comi, G., 2017. Pediatric versus adult MS: similar or different? Mult. Scler. Demyelinating Disord. 2 (1), 1–14.
Wong, Y.Y.M., de Mol, C.L., van Pelt, E.D., Ketelslegers, I.A., Catsman-Berrevoets, C.E., Neuteboom, R.F., Hintzen, R.Q., 2019. Real-world validation of the 2017 McDonald criteria for pediatric MS. Neurol.: Neuroimmunol. NeuroInflammation 6 (2).
Bunyan, R., Al Towaijri, G., Al Otaibi, H., Kareem, A., Algahtani, H., Al Mejally, M., Almubarak, A., Alrajeh, S., Cupler, E., Qureshi, S., Alawi, S., 2021. Prevalence of pediatric onset multiple sclerosis in Saudi Arabia. Mult. Scler. Int., 4226141 https://doi.org/10.1155/2021/4226141.
Alroughani, R., Boyko, A., 2018. Pediatric multiple sclerosis: a review. BMC Neurol. 18 (1), 1–8.
McMillan, S.S., King, M., Tully, M.P., 2016. How to use the nominal group and Delphi techniques. Int. J. Clin. Pharm. 38 (3), 655–662.
Rubin, J.P., Kuntz, N.L., 2013. Diagnostic criteria for pediatric multiple sclerosis. Curr. Neurol. Neurosci. Rep. 13 (6), 1–10.
Tardieu, M., Banwell, B., Wolinsky, J.S., Pohl, D., Krupp, L.B., 2016. Consensus definitions for pediatric MS and other demyelinating disorders in childhood. Neurology 87 (9 Supplement 2), S8–S11.
Pohl, D., Alper, G., Van Haren, K., Kornberg, A.J., Lucchinetti, C.F., Tenembaum, S., Belman, A.L., 2016. Acute disseminated encephalomyelitis: updates on an inflammatory CNS syndrome. Neurology 87 (9 Supplement 2), S38–S45.
Rostasy, K., Bajer-Kornek, B., Venkateswaran, S., Hemingway, C., Tardieu, M., 2016. Differential diagnosis and evaluation in pediatric inflammatory demyelinating disorders. Neurology 87 (9 Supplement 2), S28–S37.
Tenembaum, S., Yeh, E., Abboud, H., Alroughani, R., Altintas, A., Amezcua, L., Apiwattanakul, M., Asgari, N., Banwell, B., Bennett, J., Bichuetti, D., 2020. Pediatric NMOSD: a review and position statement on approach to work-up and diagnosis. Front. Pediatr. 8, 339.
Wingerchuk, D.M., Banwell, B., Bennett, J.L., Cabre, P., Carroll, W., Chitnis, T., De Seze, J., Fujihara, K., Greenberg, B., Jacob, A., Jarius, S., 2015. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 85 (2), 177–189.
Chitnis, T., Arnold, D.L., Banwell, B., Brück, W., Ghezzi, A., Giovannoni, G., Greenberg, B., Krupp, L., Rostásy, K., Tardieu, M., Waubant, E., 2018. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. N. Engl. J. Med. 379 (11), 1017–1027.
Pohl, D., Waubant, E., Banwell, B., Chabas, D., Chitnis, T., Weinstock-Guttman, B., Tenembaum, S., 2007. Treatment of pediatric multiple sclerosis and variants. Neurology 68 (16 suppl 2), S54–S65.
Rensel, M., 2019. Long-term treatment strategies of pediatric multiple sclerosis, including the use of disease modifying therapies. Children (Basel) 6 (6), 73.
Ghezzi, A., Banwell, B., Boyko, A., Amato, M.P., Anlar, B., Blinkenberg, M., Boon, M., Filippi, M., Jozwiak, S., Ketelslegers, I., Kornek, B., 2010. Meeting Review: The management of multiple sclerosis in children: a European view. Mult. Scler. J. 16 (10), 1258–1267.
Ghezzi, A., Amato, M.P., Makhani, N., Shreiner, T., Gärtner, J., Tenembaum, S., 2016. Pediatric multiple sclerosis: conventional first-line treatment and general management. Neurology 87 (9 Supplement 2), S97–S102.
Chitnis, T., Tenembaum, S., Banwell, B., Krupp, L., Pohl, D., Rostasy, K., Yeh, E.A., Bykova, O., Wassmer, E., Tardieu, M., Kornberg, A., 2012. Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis. Mult. Scler. J. 18 (1), 116–127.
Johnen, A., Elpers, C., Riepl, E., Landmeyer, N.C., Krämer, J., Polzer, P., Lohmann, H., Omran, H., Wiendl, H., Göbel, K., Meuth, S.G., 2019. Early effective treatment may protect from cognitive decline in paediatric multiple sclerosis. Eur. J. Paediatr. Neurol. 23 (6), 783–791.
L.Banwell, B., 2014. Multiple Sclerosis in Children. Handbook of Clinical Neurology, 122. Elsevier, pp. 427–441.
Lehmann, H.C., Hartung, H.P., Hetzel, G.R., Stüve, O., Kieseier, B.C., 2006. Plasma exchange in neuroimmunological disorders: Part 1: Rationale and treatment of inflammatory central nervous system disorders. Arch. Neurol. 63 (7), 930–935.
Pohl, D., Tenembaum, S., 2012. Treatment of acute disseminated encephalomyelitis. Curr. Treat. Options Neurol. 14 (3), 264–275.
Alexander, M., Murthy, J.M.K., 2011. Acute disseminated encephalomyelitis: Treatment guidelines. Ann. Indian Acad. Neurol. 14 (Suppl1), S60.
Kimbrough, D.J., Fujihara, K., Jacob, A., Lana-Peixoto, M.A., Leite, M.I., Levy, M., Marignier, R., Nakashima, I., Palace, J., de Seze, J., Stuve, O., 2012. Treatment of neuromyelitis optica: review and recommendations. Mult. Scler. Relat. Disord. 1 (4), 180–187.
Poupart, J., Giovannelli, J., Deschamps, R., Audoin, B., Ciron, J., Maillart, E., Papeix, C., Collongues, N., Bourre, B., Cohen, M., Wiertlewski, S., 2020. Evaluation of efficacy and tolerability of first-line therapies in NMOSD. Neurology 94 (15), e1645–e1656.
Damato, V., Evoli, A., Iorio, R., 2016. Efficacy and safety of rituximab therapy in neuromyelitis optica spectrum disorders: a systematic review and meta-analysis. JAMA Neurol. 73 (11), 1342–1348.
Esmaeili, S., Abbasi, M.H., Abolmaali, M., Mojtahed, M., Alavi, S.N.R., Soleimani, S., Mokhtari, M., Hatam, J., Khotbehsara, S.T., Motamed, M.R., Joghataei, M.T., 2021. Rituximab and risk of COVID-19 infection and its severity in patients with MS and NMOSD. BMC Neurol. 21 (1), 1–8.
Jacob, A., Hutchinson, M., Elsone, L., Kelly, S., Ali, R., Saukans, I., Tubridy, N., Boggild, M., 2012. Does natalizumab therapy worsen neuromyelitis optica? Neurology 79 (10), 1065–1066.
Shimizu, J., Hatanaka, Y., Hasegawa, M., Iwata, A., Sugimoto, I., Date, H., Goto, J., Shimizu, T., Takatsu, M., Sakurai, Y., Nakase, H., 2010. IFNβ-1b may severely exacerbate Japanese optic-spinal MS in neuromyelitis optica spectrum. Neurology 75 (16), 1423–1427.