

# Rituximab Use in Aggressive Pediatric Multiple Sclerosis: A Case Report

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## Abstract

Pediatric-onset Multiple Sclerosis (POMS) is a chronic inflammatory demyelinating disorder affecting the central nervous system in children. It can lead to debilitating motor and cognitive sequelae. Disease modifying therapies have been used in children as well as adults, with similarities observed in terms of tolerance, and side-effect profiles. At present the consensus in management of Pediatric MS is based mainly upon adult-based treatment trials. Multiple factors are taken into consideration, including disease activity, coexisting morbidities, patient-based preference, and socioeconomic factors. Rituximab, has shown in numerous case series and reports, to be efficient and well tolerated. We report a female child with a relapsing, progressively debilitating CNS demyelinating disease with poor compliance to Disease-Modifying therapies, and breakthrough relapses during Interferon Beta-1b and Fingolimod trials. After rituximab therapy commencement, she had shown reduction in her annualized relapse rate, improvement in her disability scores; and stability in serial neuroimaging during the subsequent 27 months of regular follow-ups.

**Keywords:** Pediatric onset multiple sclerosis (POMS), Rituximab, Neuroinflammatory disorder.

## Introduction

Pediatric-onset Multiple Sclerosis (POMS) encompasses 3-5% of the MS population, representing those with onset of MS below 18 years of age. It is a relapsing inflammatory demyelinating disorder of the central nervous system. It represents the truer onset of MS and differs from adult-onset MS in a few aspects. It is commonly a relapsing form, whose first attack might manifest as ADEM (acute demyelinating encephalomyelitis), optic neuritis, or transverse myelitis; followed by non-encephalopathic inflammatory demyelinating relapses. Pediatric MS population, although having a slower physical and motor disability when compared to adults, will develop a higher disease burden, correlating with a higher disability score with time. Early prompt intervention with appropriate disease modifying therapy represents a major part of management in helping reduce cumulative disease burden, by reducing relapse rates, and indirectly improving the patients' cognitive and neurologic functions, thereby improving the patient's function in the society and mitigating the costs of health services. Treatment approach in MS has advanced significantly during the past two decades, with the availability of new disease modifying therapies, encompassing injectable DMT (Glatiramer acetate, b-interferons), oral agents (Fingolimod, Teriflunamide, Dimethyl fumarate), and infusions (including Natalizumab, Ocrelizumab, Alemtuzumab, Rituximab, Daclizumab, Cyclophosphamide) Infusion therapies are usually reserved for highly-active multiple sclerosis with frequent relapses or significant residual deficits. Rituximab is an off-label monoclonal CD20 antibody used in systemic inflammatory disorders, which has been observed, during the past few years, with increasing use in CNS inflammatory disorders, and with promising results of efficiency and acceptable tolerance in the majority of recipients.

## Case Report

Our patient is a 14-years- old developmentally appropriate girl, who at the age of nine years, presented with acute onset diplopia, painful eye movements, and right leg and arm weakness. weakness. The event was not preceded by febrile illness or vaccination, and not associated with encephalopathy.

Her neuroimaging findings were consistent with active inflammatory demyelinating lesions in supratentorial, brainstem, and cerebellar structures. She received immunomodulation treatment in the form of a 5-day course of pulse steroids, followed by a 6-week tapering course of oral prednisolone, during which she recovered almost completely.

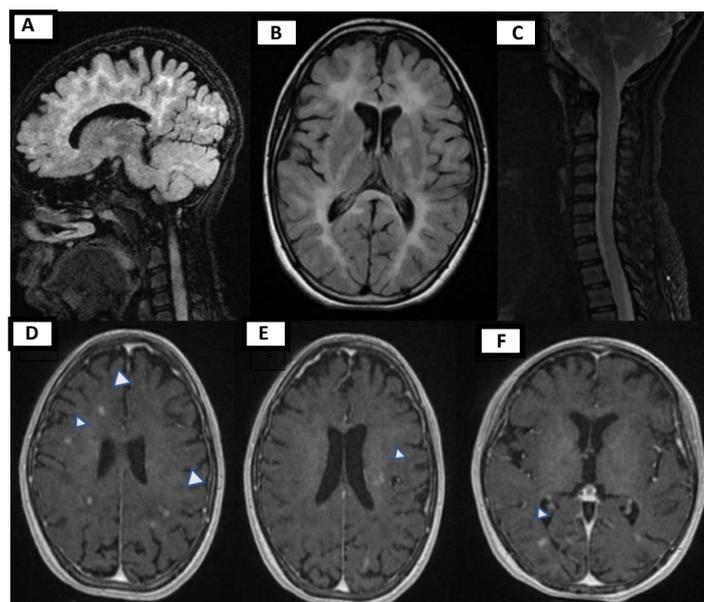
Her second relapse occurred a year later, in the form of blurring of vision in both eyes, diplopia, bilateral lower limb weakness, and numbness in lower extremities. She responded again to first-line immunomodulation, but did not recover her full strength. A 3rd and 4th relapse occurred that same year, each time prompting intervention with first-line immunotherapy at the local hospital. MRI brain serial images had shown extensive cumulative periventricular, subcortical, corpus callosum, cerebellar lesions with demyelinating characteristics. Spinal MRI had revealed cervical and thoracic short-segmented lesions. She was started on Interferon Beta-1b (Betaseron) 250 microgram SC every other day, and observed during the subsequent two years. There were compliance issues, related to injection site reactions. During that interval, she suffered 3 additional consecutive relapses. She was referred to our neuroimmunology clinic, after an unsuccessful attempt of switching to fingolimod, due to poor tolerance.

During our first assessment, patient was 12-years-old, wheel chair-bound, unable to stand supported. She had impaired short-term memory recall, slow articulation, relative afferent pupillary defect in her right eye, and bilateral optic disc pallor. She had prominent cerebellar symptoms, including unprovoked bilateral horizontal nystagmus, truncal ataxia, and moderate intention tremors on both sides. She had difficulty standing without support, and could not ambulate. Her Expanded Disability Status Scale (EDSS) score was 7.5.

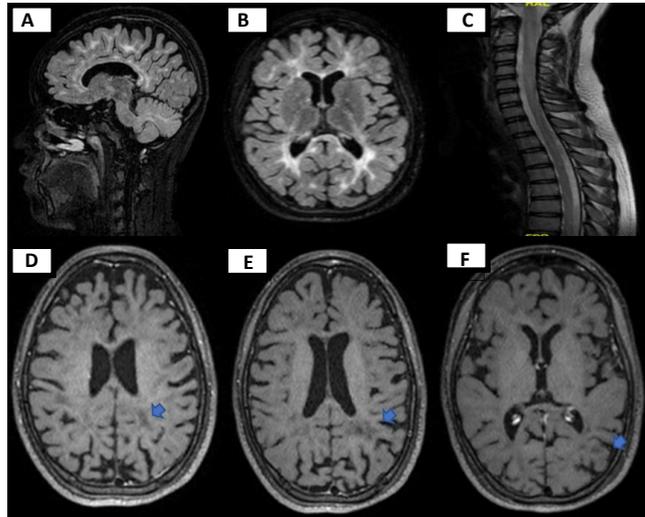
The patient was admitted, underwent CSF, serological, and follow-up neuroimaging. Her imaging had revealed a few enhancing scattered periventricular lesions, superimposed over old confluent T2 hyperintensities located in juxtacortical, deep white matter, cerebellar dentate nuclei, brainstem and in dorsal cervical and thoracic spinal cord. Her CSF oligoclonal bands were elevated, with normal serum counterpart. MOG-antibody serologic titer was borderline at (1:10), with negative aquaporin-4 antibody. CSF findings were otherwise benign. Her work-up findings were fulfilling the McDonald's criteria for relapsing multiple sclerosis.

Following investigational work-up and neuroimaging, the patient was started on 6-week tapering course of oral steroids, and induced on Rituximab 500 milligrams per meter square body surface area, two doses 14 days apart, followed by maintenance single doses at 6-month intervals. The initial neuroimaging which showed active inflammatory lesions (Figure 1), had subsequently shown resolution of the enhancement, and stability of the T2 hyperintensities. (Figure 2)

The patient had no further relapses since commencing rituximab with good tolerance, and stable CBC and immunoglobulin profile which were done bi-annually. She regained partially her gross motor and fine coordination, being able to stand up by herself, and ambulate independently for short distances. Her EDSS lowered to 5.5 compared to 7.5 pre-rituximab treatment. She resumed attending school in 6th grade.



**Figure 1:** Pre-rituximab MRI brain and cervical spine (A-B), Sagittal and Axial FLAIR views, depicting extensive periventricular confluent and subcortical T2 hyperintense lesions. Images (C) shows cervical T2 hyperintense lesions. Images (D, E, F) axial T1 contrast images of different cuts, depicting enhancing scattered periventricular lesions (points).



**Figure 2:** Images during first and second year of rituximab treatment. Figures (A-B), sagittal and axial FLAIR images, depicting stable hyperintense T2 periventricular and subcortical lesions. Figure (C) Sagittal STIR image of cervical spine: shows stable short-segmented T2 lesions. Figures (D, E, F) T1 contrast views: shows no enhancements, and T1 hypointense lesions representing atrophy and axonal loss (arrows).

## Discussion

Pediatric-onset Multiple Sclerosis (POMS) is a chronic demyelinating disease affecting the central nervous system of children under 18 years of age; If not managed early and efficiently, it has significant long-term comorbidities and outcomes in motor activity, social and cognitive function, and overall quality of life on both patient and family. (1) POMS comprises 2-10% of all multiple sclerosis (MS) cases. (1) It is characterized by comparable disease burden when compared to adult patients, when the two groups are matched for disease duration. (2)

There are no consensus guidelines in the management and treatment of pediatric multiple sclerosis, as there are no approved guidelines to date favouring specific disease-modifying therapies to others. This significant limitation of evidence-based practice makes managing such cases highly challenging.

Only two disease-modifying therapy (DMTs) (Fingolimod and teriflunomide) have been tested in large phase III trials and approved by regulatory agencies for use in POMS. (3) Interferon- $\beta$  and glatiramer acetate are commonly used as first-line therapy in the Pediatric age group with good outcomes in decreasing the disease activity.

*Rituximab* is a B cell-depleting monoclonal anti-CD20-antibody used in children's neuroinflammatory disorders. Rituximab is quite commonly used in the adult population compared to the pediatric age group in treating demyelinating disease. Multiple studies and trials showed positive effects in decreasing and controlling relapses, well-tolerated and had a lower risk of severe side effects. (4)

Most treatment approaches in the pediatric age group depend on clinical experience, and rituximab has been used as off-label in managing severely ill children with MS. However, few cases and studies reported using rituximab in the pediatric age group. (2,5-14) The Nationwide Swedish study reported 14 POMS cases with favourable outcomes of using rituximab, and around 42% of patients received rituximab as first-line therapy. They found stability in most cases and showed no evidence of disease activity, relapses or increased EDSS during the follow-up period. Only two patients out of 14 experienced rituximab failure due to skin reaction and new unenhanced MRI lesions (2). Furthermore, Clinical observation done at the University of California found that rituximab may be a viable treatment option for children with an aggressive CNS demyelinating disease course as they noticed a significant improvement in relapses of NMO and MS refractory cases after starting Rituximab therapy (2 out of 3 MS cases) has improved with no reported side effects. One patient failed to respond to treatment and required switching to other immunotherapies. (5)

In a similar case to our patient reported by Karenfort et al., a female adolescent has a worsening course of disease activity with failure of intensive therapy with various drugs (methotrexate, mycophenolate mofetil, glatiramer acetate, and interferon  $\beta$ -1a). She significantly improved after rituximab, improving her EDSS score and has the most extended relapse-free interval with no relapse since starting the infusion. (6) In addition, Parvenov et al. reported a young female with fulminant MS who was controlled on Natalizumab four years, but then was required to switch it to other DMT due to JC virus antibody conversion to seropositivity, using glatiramer acetate and Fingolimod with a poor response as, she developed frequent relapses and new enhancing lesion in brain imaging.

Rituximab was initiated with a good response with no more relapse or new lesion in MRI with improved EDSS. (7) Similarly, a reduction in relapse rate was observed in adolescents with POMS with SLE-administered rituximab. It concluded that rituximab has a potentially lower rate of adverse events compared to other treatments and safe medication and is well tolerated in managing refractory pediatric autoimmune disease. (8)

A multicenter retrospective study utilized the safety of rituximab in 144 pediatric patients with variable neuroinflammatory diseases (4 of them with POMS); the benefit was reported in 125 of 144 (87%) patients (50% of POMS), infusion adverse events were recorded in 18/144 (12.5%), eleven patients (7.6%) had an infectious adverse event. Progressive multifocal leukoencephalopathy was not recorded in the group study. (9) A prospective, open-label, phase II, multicenter study reported a superior effect of rituximab after switching from first-line injectable therapy in clinically stable RRMS cases in a reduction in inflammatory markers in CSF and inflammatory activity and contrast enhancement lesions in neuroimaging with 3,6 and 12 months to follow up. (10) Comparably, A multicenter cohort at United States Network studied large numbers of children diagnosed with MS (81%) or CIS, concluding that patients who received newer disease-modifying therapy (56/197 received rituximab) had 62% lower relapse rate compared to patients treated with injectable DMTs as well as less MRI activity. (11)

Berenguer-Ruiz has reported 12 patients diagnosed with MS, including one 19-year-old patient managed with rituximab without any clinical relapse or active lesion in neuroimaging and a stable EDSS score during the follow-up period. (12) Kornek et al. studied 11 adolescent subjects with MS who showed significant improvement with rituximab therapy with no evidence of disease activity apart from one patient with one relapse and new MRI lesion directly after the first infusion, otherwise no more signs of disease activity during patient's follow-up interval. (13) Recent similar case was reported of 12 years old boy who suffered from an aggressive course of RRMS with frequent relapses and clinical and radiological deterioration with partial recovery from each attack with EDSS of 6.5 with failure of cyclophosphamide. The patient received rituximab as a rescue therapy (375 mg/m<sup>2</sup> weekly for one month) with significant response clinically and radiologically. (14)

Our case shown dramatic improvement after initiation and maintenance of rituximab therapy for 2 years and ongoing, with no reported clinical or neuroradiologic relapses during therapy. There was also no observed infusion-related or latent side-effects, no opportunistic infections, and overall good tolerance. Also noteworthy is the return of her partial independence, and improved quality of life.

## Conclusion

This case demonstrates the effectiveness, tolerance, and availability of rituximab therapy in a pediatric patient with aggressive multiple sclerosis. Future long-term follow-up studies for investigating further the efficacy and tolerance of rituximab use in the pediatric multiple sclerosis population.

## Conflict of Interest

The authors declare no conflict of interest.

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