


## BRIEF COMMUNICATION

# T-cell depleted HLA-haploidentical HSCT in a child with neuromyelitis optica

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## Introduction

Most patients with Neuromyelitis Optica (NMO) present a relapsing course, resulting in progressive severe disability. The role of autologous hematopoietic stem cell transplantation (HSCT) has been explored in NMO resistant to conventional treatment, showing a good temporary control of the disease, but scarce results in the long term.<sup>1</sup> Greco et al. recently presented two patients with NMO successfully treated with unmanipulated allogeneic HSCT.<sup>2</sup> We report the first case of a pediatric patient with NMO, treated with HLA-haploidentical HSCT after  $\alpha\beta$  T-cell and B-cell depletion of the graft.

## Case Presentation

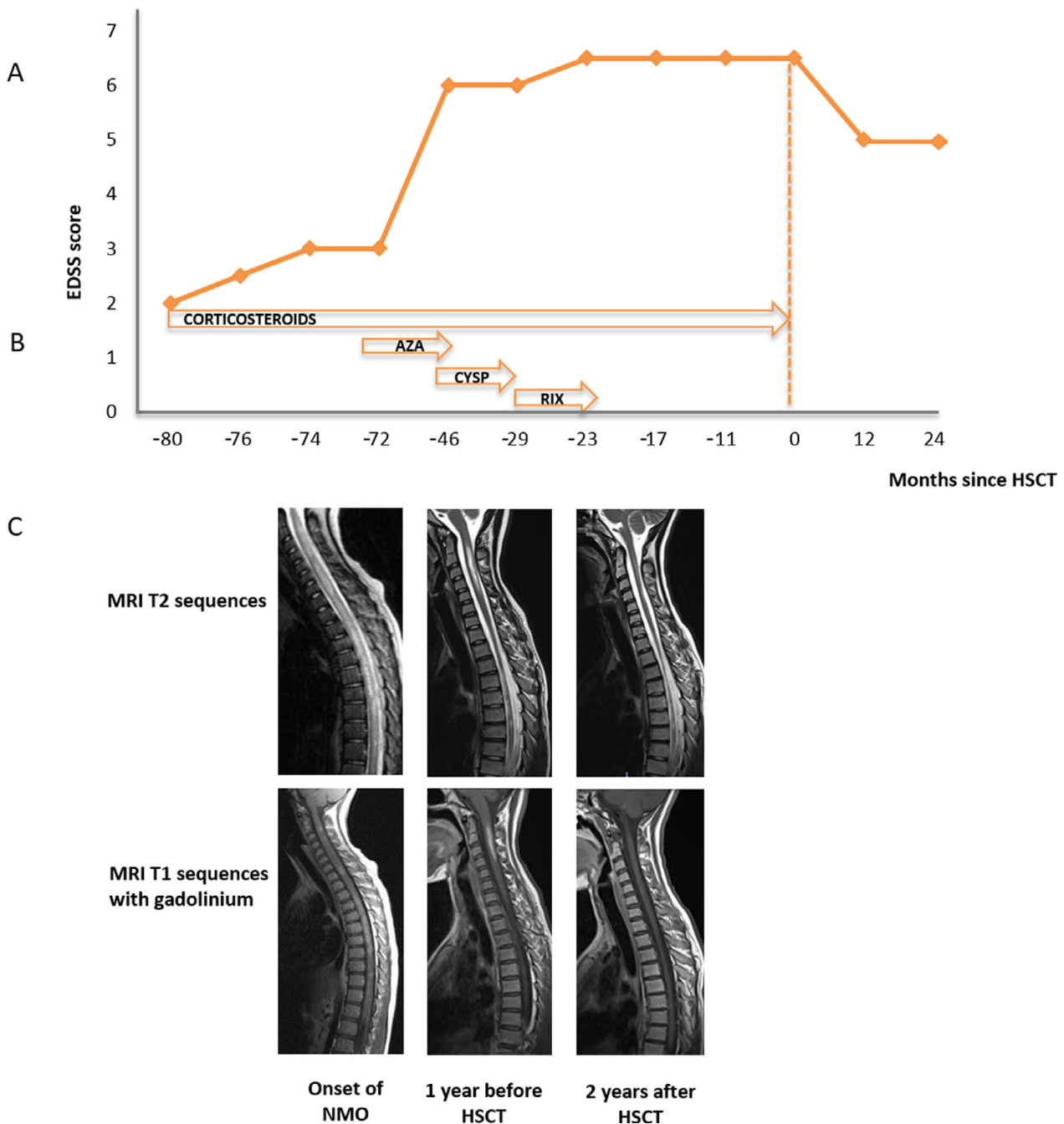
Our female patient was diagnosed at the age of 9 years. At onset, she presented bilateral optic neuritis and progressive hyposthenia at the lower limbs. Magnetic resonance

## Abstract

Neuromyelitis optica is an immune-mediated disease characterized by a relapsing course, resulting in progressive disability. In children, given the long life expectancy, a disease-modifying treatment could be particularly desirable. Unfortunately, the currently available treatment strategies with this potential are scarce. Very limited data are available about the use of allogeneic hematopoietic stem cell transplantation (HSCT) for autoimmune neurological diseases. In this report, we present a pediatric case successfully treated with allogeneic HSCT from an HLA-haploidentical donor, after ex vivo TCR/CD19-depletion of the graft. To the best of our knowledge, this is the first case of a pediatric patient to benefit from such a treatment.

imaging (MRI) showed multiple T2-hyperintense lesions in the right frontal subcortical region and corpus callosum, as well as in the cervical and dorsal spine (see Figure 1). The positivity of AQP4-autoantibodies confirmed the diagnosis of NMO. She was treated with multiple lines of therapy (including high-dose steroid, azathioprine, cyclosporine, and rituximab), without control of the disease. She experienced several relapses (Longitudinally Extensive Transverse Myelitis or optic neuritis) with annual relapse rate (ARR) of 1.5. In view of this disease course, after extensive discussion with both patient and her parents, it was decided to consider allogeneic HSCT as a potentially curative option. At the time of HSCT, the girl displayed an Expanded Disability Status Score (EDSS) of 6.5.

In accordance with the recent European Society for Blood and Bone Marrow Transplantation indications recommendations,<sup>3</sup> an allogeneic HSCT was proposed, after obtaining both approval by the local ethics committee and written informed consent from parents. Since an



**Figure 1.** Clinical and neuroradiological history of the patient. (A) Neurologic disability during the clinical follow-up, classified according to the Kurtzke Expanded Disability Status Score (EDSS). Scatter points represent relapses. The orange dashed line indicates the time of transplantation. (B) Arrows represent the therapies administered during the clinical history of the patient. (C) Neuroradiological history. Upper panels show T2-weighted sequences, lower panels T1-weighted sequences upon administration of gadolinium. Magnetic resonance imaging (MRI) at onset of symptoms showed a hyperintense T2 lesion involving the cervical spinal cord at the C2–C6 level and multiple dorsal lesion at the D2–D9 level. After gadolinium injection, the lesion shows intense enhancement. MRI performed during a relapse episode 1 year before HSCT showed an increment of cervical lesion at the C2–C6 level and unchanged dorsal lesion. After gadolinium injection, the cervical lesion shows intense enhancement. Two years after HSCT, MRI showed reduction of the T2 hyperintense spinal cord lesions, without any gadolinium enhancement. HSCT, hematopoietic stem cell transplantation; MRI, magnetic resonance imaging; AZA, azathioprine; CYSP, cyclosporine; RIX, rituximab.

HLA-matched donor, either related or unrelated, was not available, at the age of 15 years, the patient underwent HSCT from the HLA-haploidentical father. Conditioning regimen consisted of Thiotepa (10 mg/kg in 2 divided doses), Treosulfan (42 g/m<sup>2</sup> over 3 days), and Fludarabine (160 mg/m<sup>2</sup> over 4 days). Antithymocyte globulin (Grafalon®, Neovii Biotech 12 mg/kg from day -5 to -3) and rituximab (200 mg/m<sup>2</sup> on day -1) were given to tune bidirectional alloreactivity [i.e., prevention of Graft-versus-host disease (GvHD) and graft rejection] and post-transplant Epstein-Barr virus-driven B-cell lymphoproliferative disorders, respectively. GvHD prophylaxis was also performed through ex vivo negative depletion of  $\alpha\beta$  T cells from the graft.

Mobilization, leukapheresis, and graft manipulation were performed as previously described.<sup>4</sup> The graft composition was as follows: CD34+/kg 20.6  $\times$  10<sup>6</sup>; TCR  $\alpha\beta$  +/kg 0.013  $\times$  10<sup>6</sup>; TCR  $\gamma\delta$ /kg 7.17  $\times$  10<sup>6</sup>, NK cells/kg 35.2  $\times$  10<sup>6</sup>.

On day +7, the patient presented an episode of monocular amaurosis and blurred vision, successfully treated with retrobulbar injection of dexamethasone, plasma-exchange, and high-dose intravenous immunoglobulins. Neutrophil and platelet recovery occurred on day +12 and +8, respectively. Hematopoietic chimerism, serially evaluated on both peripheral blood and bone marrow cells by short tandem repeat polymerase chain reaction, showed a persistent full-donor chimerism also in sorted lymphoid cells. Details on recovery of lymphocyte subsets and immunoglobulin serum levels are shown in Table 1.

Twenty-four months after HSCT, the patient is in good general conditions, without any sign of GVHD.

The last MRI performed after 2 years from HSCT showed the absence of new lesions, and a significant reduction of preexisting lesions without gadolinium

enhancement (see Figure 1 for details). Visual evoked potentials to flash stimulation were absent before HSCT, while a low-amplitude N1/P2 response (around 4  $\mu$ V) was recorded as from 1 year after HSCT and is still persisting.

Clinically, the girl did not experience any re-exacerbation of the disease, showing a long-term stabilization. She presented a significant improvement in the EDDS, which is actually equal to 5 with return to walking without assistance.

Notably, while in the previously reported cases by Greco et al.,<sup>2</sup> serum AQP4-antibodies became negative in both patients within 6 months from transplantation, in our case, the antibodies remained positive with gradual reduction of titers on serial controls up to last follow-up after 24 months.

In patients treated with autologous HSCT, the AQP4-antibodies remained positive through the follow-up,<sup>2</sup> probably because of the incomplete elimination of long-living memory B cells. We do not exclude that such a mechanism could be responsible also for the long-term persistence of AQP4-antibodies in our patient.

## Discussion

Although the use of HSCT for autoimmune diseases (ADs) is increasing, in most disorders, it is limited to autologous HSCT. Allogeneic HSCT in ADs is now being explored and it is currently restricted to pediatric practice. This restriction probably derives from the lower risk of transplant-related fatalities observed in children as compared to adults and to the fact that the main indication are immune cytopenias, a disease mainly affecting young patients.<sup>5</sup>

From a clinical point of view, the three cases described in literature (the first two by Greco and colleagues<sup>2</sup> and the third one in this report) show an apparent superior efficacy

**Table 1.** Recovery of lymphocyte subsets (with chimerism analysis) and immunoglobulin serum levels at different time-points.

Subpopulation	3 months	6 months	12 months	24 months	Chimerism at 24 months
CD3+/ $\mu$ L	580	665	1146	1029	100%
CD3+ CD4+/ $\mu$ L	210	269	553	516	
CD4+ RA+/ $\mu$ L	1	3	93	149	
CD4+ RO+/ $\mu$ L	208	265	321	259	
Treg/ $\mu$ L	0	2	14	44	
CD3+ CD8+/ $\mu$ L	216	234	457	306	
CD8+ RA+/ $\mu$ L	5	42	166	139	
CD8+ RO+/ $\mu$ L	210	191	211	125	
TCR $\alpha\beta$ +/ $\mu$ L	424	502	1035	835	
TCR $\gamma\delta$ +/ $\mu$ L	145	161	103	178	
NK/ $\mu$ L	877	597	687	991	100%
CD19+/ $\mu$ L	0	231	252	282	100%
IgG mg/dL	780	838	936	1004	
IgA mg/dL	79	102	140	127	
IgM mg/dL	26	101	129	98	

of allogeneic HSCT in maintaining long-term disease stabilization/remission as compared to conventional treatment and/or autologous HSCT. Given these evidences and the severity of the disease, we decided not to propose an autologous HSCT but to proceed with an allograft. Since an HLA-matched either related or unrelated donor was not available, and the large experience developed in our center with  $\alpha\beta$  T-cell and B-cell-depleted HLA-haploidentical HSCT,<sup>4,6</sup> we decided to proceed with this type of allograft. We speculated that the potent myeloablative/immune suppressive regime used in allogeneic HSCT could be more effective in eliminating pathogenic memory B cells. Some animal models<sup>7,8</sup> have also postulated the existence of a sort of graft-versus-immunity effect; indeed, a subclinical graft-versus-host anti-autoimmune reaction could eradicate autoreactive B and T cells.

Since an HLA-identical family donor is available in <25% of patients,<sup>9</sup> while a fully matched unrelated donor in about 70% of Caucasian subjects (but only 16% for some ethnic minorities),<sup>10</sup> the use of haploidentical donors, as in our case, would widen the applicability of allogeneic HSCT to almost every patient with such an indication. Additional biological studies, both in vitro and in vivo, as well as more clinical data, are needed to establish the place of allogeneic HSCT in the treatment of patients with refractory NMO.

## Patient Consent

Parental/guardian consent obtained.

## Ethics Approval

Comitato Etico dell'Ospedale Pediatrico Bambino Gesù (Ethics Committee of the Bambino Gesù Childrens' Hospital).

## Author Contributions

GC, LP, and PM designed the study, GC, LP, BL, MA, SG cured the collection of the clinical data, LP, LFG, SC, MV cure the collection of the neurophysiological and the neuroimaging sections, GLP, MM cured the analysis of the immuno-hematological data, GC, PM, FL interpreted and analyzed the data, GC, LP, MV, FL, PM drafted the manuscript, MV, FL, PM revised the manuscript for intellectual content. All authors edited and approved the final draft.

## Conflict of Interest

None declared.

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