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# *SUSPECTING NEUROMYELITIS OPTICA SPECTRUM DISORDERS (NMOSD) DIAGNOSIS: DESCRIPTIVE STUDY OF A PEDIATRIC POPULATION*

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# SUSPECTING NEUROMYELITIS OPTICA SPECTRUM DISORDERS (NMOSD) DIAGNOSIS: A DESCRIPTIVE STUDY OF A PAEDIATRIC POPULATION

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**ABSTRACT**

Introduction. Neuromyelitis optica spectrum disorders (NMOSD) comprise a heterogeneous group of inflammatory and autoimmune clinical entities, involving the central nervous system with extensive demyelination, being optic neuritis and longitudinally extensive myelitis the most suggestive clinical manifestations.

Objective. This study aims to describe a paediatric cohort of patients, in which the first diagnostic impression was NMOSD, in a tertiary center, in Portugal, under Wingerchuck 2015 consensus diagnostic criteria.

Material and Methods. Patients aged less than 18 years old in which NMOSD was considered the first diagnostic hypothesis (between the years 2016 and 2019) were identified after review of the Hospital's databases. After signing an informed consent form, a retrospective and observational study was conducted, based on the collection of sociodemographic, clinical, laboratory, neurophysiological and imagological features of those patients. The ones testing negative for anti-AQP4 and anti-MOG at the first evaluation (and also those in which that information was not available for the first demyelinating event) were retested, verifying if this would modify the mentioned first diagnostic impression.

Results. Eleven patients fulfilled the inclusion criteria (10.8±6.0 years at disease onset), all Caucasian, with a male to female ratio of 1.7:1. Optic neuritis (ON) was the most common presentation (55.4%) and transverse myelitis the second most prevalent (36.4%). Most had a mild disability at presentation (EDSS 2.2±2.4). No patient presented IgG-AQP4, but 27.3% tested positive for anti-MOG IgG. Only 1 had a previously diagnosed autoimmune disorder. Steroids were the main therapeutic option (81.8% of cases), mainly in the acute phase.

Conclusion. This is the first clinical study addressing NMOSD in a Portuguese paediatric cohort, considering Wingerchuck 2015 diagnostic criteria. Data are in line with most published series, although a high prevalence of anti-MOG antibodies has been found in our population. More studies are important, with a longer follow-up period, to deepen the practical implication of this knowledge.

Key-words: neuromyelitis optica spectrum disorders; AQP4 antibodies; MOG antibodies; children; demyelination.

**RESUMO**

Introdução. O espectro da neuromielite ótica (NMOSD) engloba um grupo heterogéneo de entidades clínicas inflamatórias e autoimunes, envolvendo o sistema nervosa central com desmielinização extensa, sendo a nevrite ótica e a mielite transversa longitudinalmente extensa as suas principais manifestações clínicas.

Objetivo. Este estudo pretende descrever uma coorte de pacientes pediátricos com o diagnóstico primário de NMOSD, num centro terciário em Portugal, segundo os critérios diagnósticos do Consenso Wingerchuck 2015.

Materiais e Métodos. Pacientes com menos de 18 anos, nos quais NMOSD foi considerada a principal hipótese diagnóstica (entre 2016 e 2019) foram identificados através da pesquisa em dases de dados hospitalares. Após a assinatura do consentimento informado, foi realizado um estudo observacional retrospetivo, baseado nas características socio-demográficas, clínicas, laboratoriais, imagiológicas e neurofisiológicas dos patientes. Os que haviam testado negative para anti-AQP4 e anti-MOG na avaliação inicial – assim como os cuja informação não estava disponível à data – foram retestados, verificando se haveria modificação do diagnóstico inicial.

Resultados. Onze pacientes cumpriam os critérios de inclusão (10.8±6.0 anos à apresentação), todos de raça caucasiana, com um rácio masculino:feminino de 1.7:1. A nevrite ótica (NO) foi a apresentação mais frequente (55.4%), leguida de mielite transversa (36.4%). A maioria apresentava incapacidade ligeira (EDSS 2.2±2.4). Nenhum paciente positivou para IgG-antiAQP4, mas 27.3% apresentaram resultado positivo para anti-MOG IgG. Apenas um manifestava diagnóstico prévio de doença autoimune. Os corticoesteróides foram a opção terapêutica mais comum (81.8%), principalmente na fase aguda.

Conclusão. Este é o primeiro estudo clínico sobre NMOSD na população pediátrica em Portugal tendo em conta os critérios diagnósticos do Consenso Wingerchuck 2015. Os dados estão, globalmente, em linha com a maioria dos estudos publicados na área, ainda que se tenha detetado uma maior prevalência de anticorpos anti-MOG. Mais estudos são essenciais, com um follow-up mais longo, para aprofundar as implicações práticas destes achados.

Palavras-chave: espetro da neuromielite óptica; anti-AQP4; anti-MOG; crianças; desmielinização

## INTRODUCTION

The discovery of anti-aquaporin 4 (anti-AQP4) and anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibodies has revolutionized the diagnostic approach to a set of demyelinating diseases of the central nervous system (CNS) that, due to their singular characteristics, could not be classified within the most well-known of the diseases of this type, multiple sclerosis (MS). Distinguishing itself as a different entity, neuromyelitis optica (NMO) has been better characterized and there is already a robust body of evidence that supports its precise diagnosis, targeted complementary investigation and, of course, the therapeutic strategy to which it must be submitted (which turned out to be, in fact, very different from what is advocated for MS). Around NMO, a set of additional clinical manifestations, suggestive of demyelination of the CNS, has been causing the concept of disease spectrum to take root – NMO spectrum disorder (NMOSD) –, which makes the practical approach of these conditions extremely challenging.

This is particularly evident in the case of the paediatric population, where a disease with these characteristics naturally assumes a very low epidemiological expression, in addition to the fact that differential diagnoses can be more complex, often involving diseases that manifest very early in lifetime, which do not assume so much relevance in the adult population. For this reason, a high index of suspicion for the diagnosis of NMOSD is crucial, in order to quickly identify children and adolescents at risk of developing a serious and potentially incapacitating disease.

In this work, we aim to characterize a cohort of children and adolescents in whom, after a first suspicious clinical event, the hypothesis of NMOSD was assumed as the most likely diagnosis. The identification of serum antibodies (anti-AQP4 or anti-MOG) allowed, in some cases, that diagnosis to be confirmed. Nevertheless, the cases in which this was not possible remain as suspected/probable NMOSD cases, being under regular and frequent follow-up in our center.

## BACKGROUND

The first clinical descriptions of neuromyelitis optica spectrum disorders (NMOSD) were reported in 1894[1] by Devic and Gault in Lyon, France, documenting a population of patients with a monophasic course of bilateral optic neuritis and myelitis, with severe disability following the neurological symptoms attacks. The so-called Devic syndrome persisted as a vastly disregarded clinical entity, most patients being classified as having atypical features of a closely related condition – multiple sclerosis (MS), especially its relapsing-remitting subtype – and kept so until very recently, when evidence mounted pointing that NMOSD and MS might be different diseases, in clinical features, imaging findings and, especially, in immune phenotypes.

NMOSD is a spectrum of rare auto-immune neuroinflammatory diseases of the central nervous system (CNS), that include different clinical manifestations of a common pathological pathway, in the diagnosis of which magnetic resonance imaging (MRI) plays a fundamental role, helping to define several different phenotypes: 1) the asian optic-spinal “MS”; 2) optic neuritis or myelitis associated with distinct brain MRI lesions typical of NMOSD (with hypothalamic, corpus callosal, periventricular, or peri-ependymal brainstem lesions on T2-weighted images); 3) systemic autoimmune diseases associated with optic neuritis or myelitis; 4) single or recurrent episodes of myelitis, usually but not always involving longitudinally extensive spinal cord lesions (a spinal cord lesion on MRI involving >3 vertebral segments); 5) single or recurrent unilateral or simultaneous bilateral optic neuritis; 6) optic neuritis or transverse myelitis in isolation.

Its prevalence is hard to determine, given that population-based studies are scarce and the new consensus diagnostic criteria of Wingerchuck et.al 2015[2] (Table 1) were issued just less than 5 years ago, after the preceding consensus set in 2006[3], handing NMO diagnosis a rather rapid-changing status. Even though, world-wide prevalence is estimated, in different studies, from 0.3 to 4.4 per 100.000 inhabitants[4], being more prevalent in northern latitudes – particularly Northern Europe and North America –, extensively more common in women[5] (male:female ratio = 1:9), making up almost 85% of cases.

**TABLE 1 | 2015 Wingerchuck Diagnostic Consensus.**

| | |
|---|---|
| **NMOSD with Anti-AQP4** | **At least one core clinical characteristic** |
| | **Positive test for Anti-AQP4 using best available detection method (cell bases assay strongly recommended)** |
| | **Exclusion of alternative diagnosis** |
| **NMOSD without Anti-AQP4 or unknown Anti-AQP4 status** | **At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:**<br>- at least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETMS, or area postrema syndrome<br>- dissemination in space (2 or more different core clinical characteristics)<br>- fulfillment of additional MRI requirements, as applicable |
| | **Negative tests for Anti-AQP4 using best available detection method, or testing unavailable** |
| | **Exclusion of alternative diagnosis** |
| Core clinical characteristics | **1. Optic neuritis**<br>**2. Acute myelitis**<br>**3. Area postrema syndrome (episode of otherwise unexplained hiccups or nausea and vomiting)**<br>**4. Acute brainstem syndrome**<br>**5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions**<br>**6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions** |
| Additional MRI requirements for NMOSD without Anti-AQP4 or unknown status | 1. **Optic neuritis:** Brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over more than half of optic nerve length or involving optic chiasm<br>2. **Acute myelitis:** associated intramedullary MRI lesion extending over 3 or more contiguous segments (LETM) OR 3 or more contiguous segments of focal spinal cord atrophy in patients with a history compatible with acute myelitis<br>3. **Area postrema syndrome:** associated dorsal medulla/area postrema lesions<br>4. **Acute brainstem syndrome:** associated periependymal brainstem lesions |

The median age of onset is around 39 years (10 years more than the one of MS), with racial differences[6]: those of African or Asian ancestry had an earlier median age of onset, compared to Caucasian patients (mean 36, 33 and 44 years old, respectively). Given that the diagnosis of NMOSD with paediatric age onset is particularly challenging, establishing the significance of robust clinical diagnostic criteria for accurate early diagnosis in children and adolescents is critical, given the potential poor long-term prognosis of undiagnosed cases.

The hallmarks of NMOSD comprise essentially optic neuritis and transverse myelitis (peripheral muscle weakness, sensory losses, sphincter dysfunction), on a typically relapsing-remitting course in up to 80-90% of the patients[4], most of the remaining displaying monophasic clinical symptoms. These attacks usually develop along several days and improve throughout weeks or months, however, with various degrees of recovery – usually not complete[7].

CNS involvement is more pronounced in the optic nerve and spinal cord, but other structures can be frequently affected as well, presenting with severe persistent nausea, vomiting and hiccups (*area postrema* syndrome), daytime tiredness and narcolepsy (diencephalic syndrome), seizures and endocrine syndromes. The clinical hallmarks of these manifestations are **optic neuritis (ON)** – unilateral severe demyelination of the optic nerve, generally more severe than that of MS, but synchronous bilateral or rapidly succession of bilateral involvement is not uncommon[8], and highly suggestive of NMOSD; **brainstem syndromes** – medullary involvement outside of the spinal cord, associated with area postrema syndrome, presenting with persistent refractory nausea, vomiting, and hiccups and, rarely, acute neurogenic respiratory failure with risk of death might happen. Other manifestations span from narcolepsy and hypothermia secondary to bilateral hypothalamic lesions[9]; and **transverse myelitis (TM)** – acute demyelinating event of spinal cord grey and white matters, it is associated with perivascular inflammation by monocytes and lymphocytes, with rapid onset (from several hours to a couple of days). In contract to MS, NMOSD-TM is almost universally symmetrical, complete and with a longer extent, involving 3 or more vertebral segments, the so-called longitudinally extensive transverse myelitis (LETM).

Other organic systems than CNS can be affected in NMOSD patients, including skeletal muscle, given the presence of AQP4 in the sarcolemma, which can be targeted by circulating anti-AQP4, causing patients to complain about

recurrent muscle pain[10], and several reports of persistently elevated levels of serum creatine kinase[11] (CK) during acute attacks of NMOSD have been made. Malek et al. reported a case[12] of NMOSD onset and another of a confirmed NMOSD patient with musculoskeletal symptoms, both having significant hyperCKemia and subtle unspecific muscle biopsy histologic findings. Nevertheless, AQP4 immunoreactivity was largely diminished and complement deposits were positive. These discoveries support analogous ones[13], creating a new clinical feature. It is then plausible an NMOSD-associated myopathy, typified by the reactive attack of specific IgG against AQP4 expressed in skeletal muscle fibers, leading to transient serum CK elevations, secondary to sarcolemma damage and not by necrosis, plus musculoskeletal symptoms before NMOSD onset or new attacks. These traits were also observed in children[14].

Imaging studies (especially MRI) are other of the cornerstones of NMOSD diagnosis algorithm. In NMOSD patients, cranial MRI can be normal (except for the enhancement of optic nerve after the administration of intravenous gadolinium contrast, during optic neuritis attacks), or reveal unspecific white matter lesions, usually clinically silent[15]. Up to 10% might present with peri-ependymal white matter lesions, particularly in the hypothalamus and periaqueductal brainstem, exceptionally rich in AQP4 channels. Demyelinating lesions in the brainstem can present as isolated events or as a superior extension of cervical myelitis[16]. Spinal cord MRI is particularly useful during an attack of transverse myelitis, revealing longitudinally extensive lesions.

Not only the epidemiology and clinical features of NMOSD and MS differ, but also their pathophysiology. Whereas MS is mostly a cell-mediated disease, NMOSD is driven by a humoral-mediated inflammatory response, with serum circulation autoantibodies (IgG) against aquaporin-4 channel (anti-AQP4) and IgG MOG antibodies (anti-MOG), also present in cerebrospinal fluid (CSF), being the former, firstly reported in patients diagnosed with NMO in 2004[17], the most important immunological feature of NMOSD. NMOSD is likely a heterogeneous condition, mainly defined by 2 clinically overlapping syndromes, AQP4-associated and MOG-associated NMOSD.

AQP4 is a transmembrane water channel arising as a tetramer with two isoforms in the CNS, M1, and M23. This protein is encoded by the AQP4 gene located in 18q11.2, belonging to the family of aquaporins, being the predominant one in the brain and spinal cord. It is mostly expressed upon the basolateral

membrane domains (contrary to the apical position of most other aquaporins), facilitating water influx to the CSF, under a macromolecular complex form with excitatory amino acid transporter 2 (EAAT2), an abundant glutamine transporter in grey matter. Being derived from the diencephalon, the retina expresses high levels of AQP4, particularly on Müller cells – specific to retinal tissue. AQP4 is also expressed in skeletal muscle sarcolemma, gastric parietal cells, renal tubular epithelial cells, but in particular in CNS cells, such as astrocytes in the brain, spinal cord, and optic nerve – even during severe NMOSD attacks peripheral tissues expressing AQP4 are not as affected as the CNS. This antibody is the most sensitive and specific biomarker of NMOSD (respectively, up to 70% and 100%), giving it a crucial role in the diagnostic approach, a feature present in up to 88%[18] of NMOSD with the newest most sensitive assays.

MOG is another eminent player in demyelinating diseases other than NMOSD, e.g. recurrent ON, paediatric MS, recurrent or monophasic ON after ADEM onset (ADEM-ON) and ADEM itself, among others[19]. MOG is a glycoprotein unearthed in the CNS alone, on the outer membrane of the myelin sheath of cranial nerves, cortical neurons, and medullary nerves. Anti-MOG antibodies may be responsible for the pathogenesis of a subset of anti-AQP4 negative patients, ranging from less than 25%[20] and up to more than 40%[21] of them. However, with up-to-date data, overlaps[22,23] between anti-AQP4 and anti-MOG positiveness have not yet been found, so they may be considered mutually exclusive, for some reason not yet disclosed.

On the other hand, anti-MOG antibodies' role in pathological processes is still not completely understood[24], questions remaining about the actual role of these autoantibodies in active demyelination, or if anti-MOG might be a consequence – and not a cause – of astrocyte cytotoxicity and destruction[25]. The presence of circulating (serum or CSF) anti-MOG antibodies is associated[26] with increased risk of cerebellar and brainstem involvement, more common bilateral ON, fewer relapses and a higher chance of a monophasic presentation, a male:female ratio of 1:1, younger age at onset and a reduced residual disability.

The detection of Anti-AQP4 and anti-MOG antibodies can take place either in the serum or CSF, even though Anti-AQP4 is not produced in the CNS, but enters through weak areas of the blood-brain-barrier (BBB), such as the area postrema. These antibodies may be present in the serum years to decades before their detection in CSF and the manifestation of clinical symptoms. Along

with these antibodies, CSF may present pleocytosis with a predominance of neutrophils, and eventually the presence of oligoclonal bands, in a minority of the cases (15-30%)[4].

Beyond autoantibodies, another feature supporting the autoimmune theory behind NMOSD is its strong link with systemic autoimmune diseases[27], such as systemic lupus erythematosus (SLE), autoimmune thyroiditis, Sjögren syndrome (SS), rheumatoid arthritis, myasthenia gravis, and others, which can be comorbidities in up to 40% of the NMOSD population. In half of the patients, the detection of significant levels of related autoantibodies, such as SSA, SSB or ANA can be found, even without any clinical evidence of above-mentioned diseases.

NMOSD is an almost universally sporadic disease, however, several cases of apparent familial aggregation[28] – making up to 3% of the cases – consistent with a non-Mendelian polygenic inheritance, have been reported in recent years, giving a new path for the investigation of genetic and environmental factors, a still largely unexplored feature.

There is not a specific treatment strategy in place for NMOSD and its complications, so the approach is essentially determined by the experience in other autoimmune and demyelinating diseases, case reports and experts' opinions. The treatment comprises two phases – acute, and prophylactic or chronic. In the acute phase – attacks – the therapeutic attitude is based on intravenous (IV) steroids (IV methylprednisolone, 30 mg/kg/d to a maximum of 1,000 mg daily, for 5 to 7 consecutive days), followed by a variable period of oral prednisolone, given that studies have shown that hyperacute treatment with steroids may prevent visual loss in patients presenting with ON. Plasma exchange should be carried out in the case of a steroid-refractory patient[29], with studies showing marked improvement in motor and visual functions after 5-7 cycles[30]. Intravenous immunoglobulins – IVIg – have been used with success in up to 50% of cortico-resistant acute presentations[30], and therefore should be considered in the most defying cases and patients with absolute contraindications to steroids. In chronic phase[15], immunosuppressive therapy is essential. Azathioprine is widely used[31], reducing relapse rates in up to 89% of patients, and even full remission at 18 months for 60% of those receiving chronic therapy. Yet, rituximab plays an extremely important role when oral therapy is not sufficient to control the disease. Recently, a new agent – inebilizumab[32] –

has been proposed after a successful multicentric, double-blind, randomized placebo-controlled phase 2/3 study in adults, giving hope for the future advent of groundbreaking therapies with the potential to change the outcome of these patients.

## MATERIAL AND METHODS

We underwent an observational and retrospective study conducted in a tertiary university-associated children´s hospital (Hospital Pediátrico de Coimbra, Centro Hospitalar e Universitário de Coimbra) – making part of a multicentric registry ongoing in Portugal – comprising patients under the age of 18 years, with clinical suspicion of NMOSD diagnosis, followed in the Demyelinating Consultation of the Neuropaediatrics Unit of the Centre for Child Development.

Data collection took place from September 2019 to January 2020, investigating patients presenting to the hospital with acquired demyelinating syndromes for 3 years (January 2016 – May 2019), and simultaneously fulfilling all inclusion criteria and none of the exclusion criteria, listed below.

### Inclusion criteria

Patients with age ≤ 18 years at the time of the first clinical attack, with informed consent from them and their legal representatives and, at least, one of these: 1) idiopathic LETM episode (medullary lesion visible on MRI, with an extension of, at least, 3 contiguous vertebral segments), either isolated or recurrent; 2) optic neuritis, either recurrent or with synchronous bilateral lesions; 3) optic neuritis or LETM associated with a systemic autoimmune disease; 4) optic neuritis or myelitis, associated with cerebral lesions typical of NMOSD (hypothalamic, at the corpus callosum, periventricular or at the brainstem).

### Exclusion criteria

Either patients with criteria for another inflammatory, infectious, vascular, metabolic or demyelinating disease, or CNS malformation, or patients or legal representatives unable to provide informed consent for the study.

Using these criteria, participants were identified through observation of the clinical database of the hospital, and the informed consent was obtained ahead of the beginning of the collection of clinical data, after the authorization of the local ethical committee and the national agency for protection of private data (CNPD). Patients not yet tested for Anti-AQP4 or anti-MOG antibodies at the first clinical episode and those already tested but with a negative result were retested, with a new cell-based assay in the Immunology Laboratory of Centro Hospitalar e Universitário do Porto – Hospital de Santo António.

For all the participants, the following variables were collected: 1) sociodemographic features – age, sex, ethnicity and place of birth; 2) clinical features – the age at onset, age at definite diagnosis, clinical presentation, initial disability according to the Expanded Disability Status Scale (EDSS), dates of attacks, the topography of the attacks (optic nerve, spinal cord, brainstem, hypothalamus, and diencephalon), the severity of the attacks, the time between the attacks, number of attacks in the first year, number of attacks in the second year, annualized relapse rate, years of follow-up, progression until EDSS 3.0, 6.0, 8.0 and 10, comorbid autoimmune diseases (SLE, SS, autoimmune thyroiditis, myasthenia gravis, rheumatoid arthritis, celiac disease, other) or other comorbid disease); 3) laboratorial features – the presence of Anti-AQP4 and MOG-IgG antibodies, CSF parameters (cytology, chemistry, and oligoclonal bands); 4) imaging features – date of the exam (acute or out-of-acute phase), number, topography, and morphology of lesions, contrast enhancement; 5) neurophysiological features – visual, somatosensitive and brainstem evoked potentials; 6) therapeutical approach: acute (corticosteroids, plasmapheresis, IVIg) and chronic (azathioprine, rituximab, methotrexate, mycophenolate, other).

In statistical terms, for categorical variables, absolute and relative frequencies were used, whereas mean, standard deviation, minimum and maximum were applied for continuous variables. All statistical data analysis was completed using Statistical Package for the Social Sciences® (SPSS®), version 25.

## RESULTS

A total of 11 patients (n=11) were included in the study, 7 (63.3%) being male and 4 (36.4%) female, with an approximate male-to-female ratio of 1.74:1. The mean age at the time of data collection was 12.6±5.7 years, and 10.8±6.0 years at disease onset and diagnosis, with an average duration of the first clinical attack of 8.5±9.4 days. All of the patients were Caucasian, born and living in Portugal. Table 2 summarizes this cohort's characteristics.

**TABLE 2 | Sample's basal characterization.**

| Characteristics | N | % (n) or Mean±SD | Minimum - Maximum |
|---|---|---|---|
| **Gender** | 11 | | |
| **Male** | | 63.6 (7) | |
| **Female** | | 36.4 (4) | |
| **Age (years)** | 11 | 12.6±5.7 | 3.0-19.0 |
| **Age at disease onset (years)** | 11 | 10.8±6.0 | 0.9-18.0 |
| **Age at diagnosis (years)** | 11 | 10.8±6.0 | 0.9-18.0 |
| **Symptoms duration (days)** | 11 | 8.5±9.4 | 0.0-30.0 |
| **First symptom** | 11 | | |
| **Optic neuritis** | | 54.5 (6) | |
| **Transverse myelitis** | | 36.4 (4) | |
| **Supratentorial signs** | | 9.1 (1) | |
| **Anti-AQP4 antibodies (serum)** | 9 | 0 | |
| **Anti-MOG antibodies (serum)** | 8 | 37.5 (3) | |
| **Cerebrospinal fluid (at 1st presentation)** | 7 | | |
| **Normal cell analysis** | | 57.1 (4) | |
| **≤15 cells/mL** | | 14.3 (1) | |
| **>15 cells/ml** | | 28.6 (2) | |
| **Mononuclear cells** | 7 | 42.9 (3) | |
| **Clinical lesions topography** | 11 | | |
| **Optic neuritis** | | 54.5 (6) | |
| **Spinal cord** | | 45.5 (5) | |
| **Time between events (months)** | 3 | 14.0±9.8 | 6.0-25.0 |
| **Events** | | | |
| **At 12 months** | 11 | 1.2±0.4 | 1.0-2.0 |
| **At 24 months** | 10 | 0.2±0.4 | 0.0-1.0 |
| **Annualized relapse rate (at 24 months)** | 10 | 0.7±0.3 | 0.5-1.0 |
| **During follow-up** | 11 | 1.3±0.5 | 1.0-2.0 |
| **Follow-up (years)** | 10 | 1.8±1.1 | 0.1-3.0 |
| **EDSS at disease onset** | 11 | 2.2±2.4 | 0.0-5.5 |
| **Comorbidities** | 10 | 70.0 (7) | |
| **Autoimmune diseases** | 11 | 9.1 (1) | |

EDSS, Expanded Disability Status Scale; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; N, number of patients with available data; SD, standard deviation.

As previously said, all these patients presented with a clinical manifestation that raised the diagnostic possibility of NMOSD, according to current consensus diagnostic criteria[2]. The most common clinical presentation at disease onset was optic neuritis in 54.5%, with a minority of cases presenting

with spinal symptoms (45.5%), most of them with LETM (36.4%). Only 3 out of the 11 patients (27.3%) had 2 or more attacks during the follow-up period, with a mean time between events of 14.0±9.8 months. All of the patients had at least one event during the first year of follow-up (1.2±0.4) and only 2 had events in the second year, making up an annualized relapse rate (at 24 months) of 0.7±0.3. The total follow-up ranged between 1 and 2 years, with an average of 1.8±1.1 years.

At disease onset, the mean EDSS score was 2.2±2.4, ranging from 0 to 5.5. Seventy percent of studied patients had comorbidity, comprising AHDH (attention deficit and hyperactivity disorder) (n=1, 9.1%), Scheurmann syndrome (n=1, 9.1%), depressive syndrome (n=1, 9.1%), retinian drusens (n=1, 9.1%) and familial hypercistinemia (n=1, 9.1%). Only 1 patient (9.1%) had an autoimmune disorder – intermediate uveitis and arthritis, suggestive of the diagnosis of juvenile rheumatoid arthritis – diagnosed before NMOSD onset.

At first clinical presentation, 9 out of 11 patients (81.2%) were tested for IgG-AQP4 antibodies in serum samples, and 8 foranti-MOG IgG antibodies. The first were not present in any of the subjects, while the latter was identified in 3 out of 8 patients (37.5%). As previously said, for patients who, at the first clinical manifestation, were not tested for any of these antibodies and also for those whose results were initially negative, a second determination was made by a new generation cell-based assay, in a reference laboratory (sampling was not performed in any period of clinical exacerbation – out-of-phase blood samples). All of the patients retested were defined as negatives for each one of the antibodies, so there was no change in the diagnosis imposed by this new laboratory test, giving a final prevalence of positive antibody testing in this population of 0.0% for IgG-AQP4 antibodies and 27.3% (3 out of 11) for anti-MOG IgG antibodies.

In the CSF studies performed at presentation (n=7), 42.9% (n=3) showed pleocytosis, in all of them due to mononuclear cell predominance. Oligoclonal bands were not identified in any of the patients.

Table 3 contains the imaging features of the studied population.

**TABLE 3 | Imaging features**

| Characteristics | Acute Brain MRI | | Acute Spinal MRI | | Out-of-phase Brain MRI | | Out-of-phase Spinal MRI | |
|---|---|---|---|---|---|---|---|---|
| | N | % (n) | N | % (n) | N | % (n) | N | % (n) |
| **Findings** | 11 | | 8 | | 8 | | 5 | |
| **Normal** | | 27.2 (3) | | 50.0 (4) | | 37.5 (3) | | 60.0 (3) |
| **Unspecific** | | 27.2 (3) | | 0.0 (0) | | 25.0 (2) | | 20.0 (1) |
| **NMOSD-like** | | 45.5 (5) | | 50.0 (4) | | 37.5 (3) | | 20.0 (1) |
| **Number of lesions** | 8 | | 4 | | 6 | | 2 | |
| **1-10** | | 87.5 (7) | | 100.0 (4) | | 83.3 (5) | | 100.0 (2) |
| **11-20** | | 0.0 (0) | | 0.0 (0) | | 0.0 (0) | | 0.0 (0) |
| **>20** | | 12.5 (1) | | 0.0 (0) | | 16.6 (1) | | 0.0 (0) |
| **Topography** | 8 | | 4 | | 6 | | 2 | |
| **LETM** | | N/A | | 100.0 (4) | | N/A | | 100.0 (2) |
| **Optic nerve** | | 50.0 (4) | | N/A | | 33.3 (2) | | N/A |
| **Brain/brainstem** | | 62.5 (5) | | N/A | | 66.6 (4) | | N/A |
| **Contrast uptake** | 7 | 42.9 (3) | 4 | 25.0 (1) | 8 | 25.0 (2) | 2 | 50.0 (1) |

LETM, longitudinally extensive transverse myelitis; MRI, magnetic resonance imaging; N, number of patients with available data; NMOSD, neuromyelitis optica spectrum disorder.

Considering the acute phase, all of the 11 patients were submitted to a brain MRI at the time of disease onset, of which 3 (27.2%) had unspecific findings and 5 (45.5%) NMOSD-suggestive findings, and 3 (27.2%) showed normal imaging studies. The most common topography was the brain/brainstem with 62.5% (5 out of 8) of the cases, followed by the optic nerve in 50% of abnormal MRIs, given that one of the patients had simultaneously brain/brainstem lesions and optic neuritis. Out of the 8 patients with abnormal MRI, 87.5% had between 1 and 10 lesions. Contrast uptake was revealed in 42.9% of those exposed. Eight patients were submitted to a spinal MRI at the time of disease onset, of which an equal number of cases had normal studies (n=4) and NMOSD-like findings (n=4). Considering the 4 patients with abnormal MRI, all had between 1 and 10 lesions. Contrast uptake was revealed in 25.0% of those exposed.

Regarding the out-of-phase/chronic evaluation, of the 11 patients, 8 underwent a brain MRI after symptoms resolution, of which only 3 (37.5%) showed a normal MRI. The most common lesion topography was brain/brainstem with 66.6% of the cases, followed by optic nerve with 33.3%. From the 6 patients with abnormal MRI, 83.3% had between 1 and 10 lesions. Contrast uptake was revealed in 25.0% of those exposed. Five patients were submitted to a spinal MRI after disease onset, of which 60.0% had normal findings and an equal number of cases had unspecific (n=1) and NMOSD-like features (n=1). From the 2 patients with abnormal spinal MRI, all had between 1 and 10 lesions. Contrast uptake was revealed in 50.0% of those exposed.

In our cohort, only 3 patients (27.2%) were submitted to a neurophysiological evaluation with visual evoked potentials. Only 1 (33.3%) had abnormal findings, as presented in Table 4.

**TABLE 4 | Visual Evoked Potentials**

| Visual Evoked Potentials | N | % (n) |
|---|---|---|
| **Performed** | 3 | 100.0 (3) |
| **Status** | 3 | |
| **Abnormal** | | 33.3 (1) |
| **Normal** | | 66.7 (2) |

N, number of patients with available data.

Table 5 contains the information related to therapeutic strategies that were considered for this cohort of patients.

**TABLE 5 | Therapeutic strategies**

| Characteristics | N | % (n) or Mean±SD |
|---|---|---|
| **Acute phase therapy** | 11 | |
| **Steroids** | | 81.8 (9) |
| **Steroids dosage (mg)** | | 781.3±335.3 |
| **Immunoglobulin (IVIg)** | | 27.3 (3) |
| **Immunoglobulin dosage (grams)** | | 184.0±210.7 |
| **Chronic therapy** | 11 | 9.1 (1) |
| **Number of attempted drugs** | 11 | 1.2±0.8 |

N, number of patients with available data; SD, Standard deviation.

During clinical attacks, steroids were the most common drug used (n=9; 81.9%) with a mean maximum dose of 781.3±335.3 mg (methylprednisolone was the drug of choice for all cases) and 3 patients (27.3%) were treated with IVIg with a mean maximum dose of 184.0±210.7 g.

Only 1 of the 11 patients (9.1%) is under chronic treatment, with azathioprine, at a dose of 75 mg per day. The average number of attempted drugs for disease remission was 1.2±0, with 2 out of 11 (18.2%) needing a combination of steroids and IVIg, at least for a certain period.

## DISCUSSION

The present descriptive study is one of the very few addressing NMOSD in the Portuguese population, and the first to focus on the paediatric age only. Additionally, it is important to note that the first and only multicentric study in Portugal[33] was completed under the, now outdated, 2006 diagnostic criteria[3], whereas our study is the first, in Portugal, to comply with the most recent 2015 criteria[2].

Given that the average age at NMOSD onset is around the 3rd to 4th decade of life, and paediatric-onset is present in a generally small subset of patients, descriptive studies focusing on paediatric NMOSD are very scarce, and NMOSD is still a largely underrecognized clinical entity around the globe. Epidemiological features and clinical presentations are similar enough to MS and other demyelinating diseases more prevalent than NMOSD to create a possible misdiagnosis with these entities, especially in children. However, in recent years, this group of diseases might be under crescent recognition, given the publication of some population-based studies[34,35,36,37,38,39].

Our results are generally similar to those of cited cohort studies, even though with some differences, such as the lower mean age at onset (10.8 years in our case, instead of 12-14 years[36,38,39]), the male:female ratio (male predominance in our study, whereas most studies present with a clear female predominance[37,38]), and ethnicity, since all our patients are Caucasian. The most common clinical presentation was optic neuritis (54.5%), as in all the mentioned studies, followed by spinal symptoms with LETM predominance.

Probably due to the short follow-up period, EDSS score progression was not present in any of our patients, with a mean EDSS at the presentation of 2.2±2.4, ranging from 0 to 5.5, and all cases had a reduction in EDSS score right after acute therapy. Therefore, the mean progression index (PI) in EDSS verified in most studies[34,37] was not verified in our cohort, even though just one patient needed chronic therapy. Differently from previous findings, 72.7% of our population had a monophasic disease (so far), the remaining 27.3% having a relapsing-remitting course, with a mean time between attacks of 14.0±9.8 months – most studies showed a dominant relapsing-remitting course[33,37,40] and no cases of a progressive course, also in line with a previous Portuguese study[33].

The annualized relapse rate was 0.7±0.3 in our population, very similar to findings in Brazilian studies[37,40]. The total follow-up ranged between 1 and 2 years, with an average of 1.8±1.1 years, contrasting with long follow-up times in many international studies, ranging up to 10 years.

More than two-thirds of our population had at least one comorbid disease, but only 1 presented an autoimmune disorder, namely a possible juvenile rheumatoid arthritis, that had been diagnosed before NMOSD onset. This is also consistent with findings of other studies, in which the prevalence of other autoimmune (AI) conditions ranges from 5 to 10%[41,42], even though, as stated above, rheumatoid arthritis was not one of the most common AI diseases found. The premature age of this population might play a role in the low prevalence of associated AI diseases, given that most of them first present in late adolescence or early adulthood.

Unlike most of the descriptive studies available, our population did not present anti-AQP4 antibodies but showed a higher prevalence of anti-MOG antibodies than most of the cohorts described. This finding might explain several features, such as lower age at disease onset, fewer residual disability (as measured by the EDSS score) and a higher male prevalence[24,25,26]. This is a very interesting detail, which deserves further investigation, particularly regarding the long-term monitoring of this cohort.

Regarding neurophysiological studies, only visual evoked potentials were provided, and excusively to patients presenting with visual symptoms and/or imaging studies compatible with optic neuritis (ON), in which the clinical diagnosis was not very clear. As stated in the scarce literature[43,44], a significant majority of ON patients had abnormal findings (low wave amplitude and increased P100 latency), confirming the functional injury of the optic nerve. Our data does not allow any consideration of the possible asymptomatic involvement of the optic nerve in these patients since the neurophysiological examination was not done systematically in this cohort.

Findings related to CSF analyses were also similar to diverse studies when it comes to both cellular content (pleocytosis in almost half of the patients with mononuclear predominance), and the absence of oligoclonal bands[8,45] – in opposition to a vast list of demyelinating diseases, such as the closely related MS.

This study had limitations worth mentioning. Due to the low incidence of NMOSD, being still largely underrecognized, and owing to the study being done in just one of the 3 major Paediatric Hospitals in Portugal, the recruited population was unavoidably small, even though, aligning with studies in countries with a similar population. Not all children underwent both brain and spinal imaging studies on 2 different occasions (acute and chronic phases), therefore creating restraint in the analysis of the evolution of imaging patterns in both normal and abnormal MRIs. Given the young age of the study population, most of them were not submitted to several diagnostic tests, such as lumbar puncture for CSF analysis, evoked potentials and determinations of circulating autoimmune antibodies (other that AQP4 and MOG), creating another limitation in the full characterization of the cohort.

Even so, a descriptive study with these characteristics allows for a good analysis of the state of the art regarding the recognition and characterization of a rare disease, in a very challenging patient population.

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## CONCLUSION

As a rare group of clinical entities, NMOSD remains a largely under-recognized disease, both at presentation and during the first years of progression, especially in the paediatric population. The clinical, imaging and additional extensive descriptional characterization of our population was overall comparable to most of the available literature on the topic, even though we found a lower mean age at presentation, a male preponderance (contrary to almost all recent papers) and no EDSS progression (so far).

More studies, with bigger populations, long prospective follow-up and active characterization are suggested, in order to better comprehend the effects of these conditions, when they start so early in life, at paediatric age.

## SCIENTIFIC PRESENTATION

The present work was submitted as an abstract - awaiting for evaluation - for the following congresses:

- 4th International Paediatric Neurology Congress, Dubai, 2020
- 5th World Summit on Paediatrics, Lisbon, 2020

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# ATTACHMENTS´

## ATTACHMENT 1 | EDSS disability score

According to Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33(11):1444-52.

| **EDSS SCORE** | |
|---|---|
| **0** | Normal neurological exam (all grades 0 in Functional Systems [FS]; cerebral grade 1 acceptable). |
| **1.0** | No disability, minimal signs in one FS (ie, grade 1, excluding cerebral grade 1) |
| **1.5** | No disability, minimal signs in more than one FS (more than one grade 1 excluding cerebral grade 1). |
| **2.0** | Minimal disability in one FS (one FS grade 2, others 0 or 1). |
| **2.5** | Minimal disability in two FS (two FS grade 2, others 0 or 1). |
| **3.0** | Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory. |
| **3.5** | Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1). |
| **4.0** | Fully ambulatory without aid, self-sufficient, up and about some twelve hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 500 meters. |
| **4.5** | Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance, characterised by relatively severe disability, usually consisting of one FS grade 4 (others grade 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 300 meters. |
| **5.0** | Ambulatory without aid or rest for some 200 meters; disability severe enough to impair full daily activities (e.g. to work a full day without special provisions). (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0). |
| **5.5** | Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0). |
| **6.0** | Intermittent or unilateral constant assistance (cane, crutch, or brace) required |

| | |
|---|---|
| | to walk about 100 meters with or without resting. (Usual FS equivalents are combinations with more than two FS grade 3+). |
| **6.5** | Constant bilateral assistance (cane, crutch, or brace) required to walk about 20 meters without resting. (Usual FS equivalents are combinations with more than two FS grade 3+). |
| **7.0** | Unable to walk beyond 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day. (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely, pyramidal grade 5 alone). |
| **7.5** | Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorised wheelchair. (Usual FS equivalents are combinations with more than one FS grade 4+). |
| **8.0** | Essentially restricted to bed or chair or perambulated in wheelchair; but may be out of bed itself much of the day; retains many self-care functions; generally, has effective use of arms. (Usual FS equivalents are combinations, generally grade 4+ in several systems). |
| **8.5** | Essentially restricted to bed much of the day; has some effective use of the arm(s); retains some self-care functions. (Usual FS equivalents are combinations, generally grade 4+ in several systems). |
| **9.0** | Helpless bed patient; can communicate and eat. (Usual FS equivalents are combinations, mostly grade 4+ in several systems). |
| **9.5** | Totally helpless bed patient; unable to communicate effectively or eat/swallow. (Usual FS equivalents are combinations, almost all grade 4+). |
| **10.0** | Death |

**ATTACHMENT 2 | Information for the patient**

**FOLHA DE INFORMAÇÃO AO PARTICIPANTE SOBRE O ESTUDO**

**"DOENÇAS MEDIADAS POR ANTICORPOS ANTI-AQP4 E ANTI-MOG: ESTUDO DESCRITIVO DE UMA POPULAÇÃO PEDIÁTRICA"**

Este documento informativo destina-se ao esclarecimento do estudo que lhe vai ser proposto realizar, contendo informações sobre as características e objectivo do estudo e uma declaração de consentimento que deverá assinar caso decida participar. A este tipo de documento dá-se o nome de consentimento informado.

**OBJETIVO DO ESTUDO**

Este estudo, que envolve a participação dos principais hospitais portugueses, pretende investigar as características da população pediátrica com NMOSD em relação às suas características demográficas, clínicas, analíticas e imagiológicas.

**CARACTERÍSTICAS DO ESTUDO**

O estudo em causa visa a recolha de informação através da consulta do processo clínico do doente. Serão aplicados questionários e efetuada colheita de sangue aos doentes que não tenham realizado ainda o teste para os anticorpos associados a esta doença NMO, ou naqueles em que o dito teste tenha sido negativo. Está prevista a recolha, processamento e publicação destes dados para fins de investigação médica.

A participação do doente neste estudo é totalmente voluntária, pode decidir abandonar o estudo a qualquer momento, sem explicar o motivo, e sem perder direitos à assistência médica como doente. Os investigadores e os doentes que aceitem participar não receberão qualquer compensação financeira e não terão nenhum gasto adicional decorrente da sua participação no estudo.

Os dados pessoais e de saúde permanecerão confidenciais - o seu nome não será incluído em formulários, relatórios ou em publicações. O presente estudo foi submetido a aprovação pela Comissão de Ética do Centro Hospitalar e Universitário de Coimbra e pela Comissão Nacional de Proteção de Dados.

Antes de assinar este consentimento, deve colocar as questões ou dúvidas que pretender. A equipa do estudo está apta a responder a questões antes, durante e após o estudo.

Se tiver questões sobre este estudo deve contactar:

Grupo de trabalho: Filipe Palavra (914632128)

**ATTACHMENT 3 | Written Informed Consent**

**TERMO DE CONSENTIMENTO INFORMADO**

Eu, abaixo-assinado (NOME COMPLETO DO INDIVÍDUO PARTICIPANTE DO ESTUDO) ou Eu, abaixo-assinado (nome completo do representante legal do indivíduo Participante do estudo), na qualidade de representante legal de (NOME COMPLETO DO INDIVÍDUO PARTICIPANTE DO ESTUDO) [conforme o caso]:

Fui informado de que o Estudo de Investigação acima mencionado se destina a investigar as características da população portuguesa com NMOSD em relação às suas características demográficas, clínicas, analíticas e imagiológicas.

Sei que neste estudo está prevista a realização de recolha de informação através da consulta do processo clínico do doente. Serão aplicados questionários e no dia da consulta será efetuada colheita de uma amostra de sangue aos doentes que não tenham realizado ainda o teste para os anticorpos associados a esta doença NMO, tendo-me sido explicado em que consistem e quais os seus possíveis efeitos.

Sei que uma parte do sangue vai ser enviada para um laboratório externo ao CHUC, onde a amostra vai ser utilizada de imediato para fazer algumas análises e que outra parte vai ser armazenada para ser utilizada posteriormente.

Foi-me garantido que todos os dados relativos à identificação dos Participantes neste estudo são confidenciais e que será mantido o anonimato.

Sei que posso recusar-me a participar ou interromper a qualquer momento a participação no estudo, sem nenhum tipo de penalização por este facto ou Sei que posso recusar-me a autorizar a participação [conforme o caso] ou interromper a qualquer momento a participação no estudo, sem nenhum tipo de penalização por este facto.

Compreendi a informação que me foi dada, tive oportunidade de fazer perguntas e as minhas dúvidas foram esclarecidas.

Aceito participar de livre vontade no estudo acima mencionado ou Autorizo de livre vontade a participação daquele que legalmente represento no estudo acima mencionado. [conforme o caso]

Concordo que seja feita a colheita duma amostra de sangue para realizar as análises que fazem parte deste estudo.

Também autorizo a divulgação dos resultados obtidos no meio científico, garantindo o anonimato.

Participante no estudo (se idade superior a 16 anos)

| Data | Assinatura |
|---|---|
| ___/___/_____ | _____ |

Representante Legal do Participante no Estudo

| Data | Assinatura |
|---|---|
| ___/___/_____ | _____ |

Médico Responsável ou Nome do Investigador Responsável

| Data | Assinatura |
|---|---|
| ___/___/_____ | _____ |

**ATTACHMENT 4 | Authorization from CNPD – National Commission for Data Protection**

**Autorização n.º 11048/ 2017**

Maria Ernestina Azevedo Moreira Santos notificou à Comissão Nacional de Protecção de Dados (CNPD) um tratamento de dados pessoais com a finalidade de realizar um Estudo Clínico sem Intervenção, denominado Doenças do Espetro da Neuromielite Óptica em Portugal (NMOSD) Registo multicêntrico .

A investigação é multicêntrica, decorrendo, em Portugal, nos centros de investigação identificados na notificação.

Existe justificação específica, validada pela Comissão de Ética Competente (CEC), para o tratamento do dado pessoal raça/etnia.

Existe justificação específica para o tratamento de dados comportamentais, psicológicos ou volitivos, os quais estão diretamente relacionados com a investigação.

O participante é identificado por um código especificamente criado para este estudo, constituído de modo a não permitir a imediata identificação do titular dos dados; designadamente, não são utilizados códigos que coincidam com os números de identificação, iniciais do nome, data de nascimento, número de telefone, ou resultem de uma composição simples desse tipo de dados. A chave da codificação só é conhecida do(s) investigador(es).

É recolhido o consentimento expresso do participante ou do seu representante legal. A informação é recolhida diretamente do titular e indiretamente do processo clínico.
As eventuais transmissões de informação são efetuadas por referência ao código do participante, sendo, nessa medida, anónimas para o destinatário.

A CNPD já se pronunciou na Deliberação n.º 1704/2015 sobre o enquadramento legal, os fundamentos de legitimidade, os princípios aplicáveis para o correto cumprimento da Lei n.º 67/98, de 26 de outubro, alterada pela Lei n.º 103/2015, de 24 de agosto, doravante LPD, bem como sobre as condições e limites aplicáveis ao tratamento de dados efetuados para a finalidade de investigação clínica.

No caso em apreço, o tratamento objeto da notificação enquadra-se no âmbito daquela deliberação e o responsável declara expressamente que cumpre os limites e condições aplicáveis por força da LPD e da Lei n.º 21/2014, de 16 de abril, alterada pela Lei n.º 73/2015, de

27 de junho – Lei da Investigação Clínica –, explicitados na Deliberação n.º 1704/2015.

O fundamento de legitimidade é o consentimento do titular.

A informação tratada é recolhida de forma lícita, para finalidade determinada, explícita e legitima e não é excessiva – cf. alíneas a), b) e c) do n.º 1 do artigo 5.º da LPD.

Assim, nos termos das disposições conjugadas do n.º 2 do artigo 7.º, da alínea a) do n.º 1 do artigo 28.º e do artigo 30.º da LPD, bem como do n.º 3 do artigo 1.º e do n.º 9 do artigo 16.º ambos da Lei de Investigação Clínica, com as condições e limites explicitados na Deliberação da CNPD n.º 1704/2015, que aqui se dão por reproduzidos, autoriza-se o presente tratamento de dados pessoais nos seguintes termos:

**Responsável –** Maria Ernestina Azevedo Moreira Santos

**Finalidade –** Estudo Clínico sem Intervenção, denominado Doenças do Espetro da Neuromielite Óptica em Portugal (NMOSD) Registo multicêntrico

**Categoria de dados pessoais tratados –** Código do participante; idade/data de nascimento; género; raça/etnia; dados antropométricos; sinais vitais; dados da história clínica; dados dados de exame físico; dados de meios complementares de diagnóstico; medicação prévia concomitante; comportamentais, psicológicos ou volitivos com conexão com a Investigação

**Exercício do direito de acesso –** Através dos investigadores, presencialmente

**Comunicações, interconexões e fluxos transfronteiriços de dados pessoais identificáveis no destinatário –** Não existem

**Prazo máximo de conservação dos dados –** A chave que produziu o código que permite a identificação indireta do titular dos dados deve ser eliminada 5 anos após o fim do estudo.

Da LPD e da Lei de Investigação Clínica, nos termos e condições fixados na presente Autorização e desenvolvidos na Deliberação da CNPD n.º 1704/2015, resultam obrigações que o responsável tem de cumprir. Destas deve dar conhecimento a todos os que intervenham no tratamento de dados pessoais.

Lisboa, 29-09-2017

A Presidente, Filipa Calvão.