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Acute Inflammatory myelitis: a 10-year clinical review

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Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

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Dedicatória

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Um obrigada do fundo do coração.

Filipa

Acute inflammatory myelitis – a 10-year clinical review

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Abstract

Background: Myelitis is an inflammatory condition that affects spinal cord (SC) and can be a clinical presentation of many diseases affecting the Central Nervous System (CNS). Though Multiple Sclerosis (MS) is the most recognized, other clinical entities may also be a cause of myelitis, so we aim to characterize each entity and its impact in the future of patients.

Aim: To characterize clinical and paraclinical findings and follow-up data of patients admitted to a Portuguese university hospital ward, presenting an acute first inflammatory myelitis episode.

Methods: The study was designed as a retrospective analysis of all adult patients with a first episode of myelitis, admitted to the ward of Neurology Department of Centro Hospitalar Universitário São João (CHUSJ), EPE, Portugal, from 1st January of 2007 to 31st December of 2016. Statistical analysis comprised descriptive statistics as well as ANOVA, Mann-Whitney U, Kruskal-Wallis, chi-square, Fisher's exact and Bonferroni correction tests, using SPSS Software V.25 and *p* values <0,05 were considered of statistical significance. Odds Ratio (OR) was the measure of association used.

Results: Of 244 acute SC syndromes identified, 71 were included as a first myelitis event. MS, including Clinically isolated syndrome (CIS), was the most frequent diagnosis established (66,2%) Were found statistically significant differences concerning autonomous walking (p<0,001), sphincter dysfunction (p=0,002), pain (p=0,011) among MS/CIS *vs* other diagnostic entities. Related to MSSS results were found statistically significant differences when comparing MS/CIS *vs* Neuromyelitis optica spectrum disorders (NMOSD) patients (p=0.011). In what concerns follow-up, 19 (26,8%) patients had a full recovery and 34 (49,3%) had a relapse of its pathology, showing statistically significant differences among etiologies (p=0,013). The association of having MSSS > 2,5 at last appointment and presence of motor symptoms (OR=5,24 [1,74-15,87]) and walking impairment (OR=2,88 [1,73-4,80]) at inaugural episode were evaluated, as well as MSSS > 2,5 and evidence of myelitis relapses (OR=1,80 [1,01-3,21]).

Conclusion: Traducing different pathological processes, clinical and paraclinical signs evaluated have differences between MS/CIS group and other etiologies. Considering the low rate of full recovery, these disorders represent an important cause of impairment and, therefore, we should recognize and act promptly to reduce their burden.

Keywords: inflammatory myelopathy, myelitis, demyelinating disease, multiple sclerosis, neuromyelitis optica spectrum disorders, idiopathic acute transverse myelitis

Highlights:

- Myelopathies can be caused by multiple etiologies, including inflammatory.
- MS is the most prevalent and studied cause of inflammatory myelitis.
- Not all causes of myelitis have the same course of disease and prognosis.
- Clinical features at presentation are important predictors for long-term prognosis.

Abbreviations

SC – Spinal Cord

CNS – Central Nervous System

MS – Multiple Sclerosis

CIS – Clinically isolated syndrome

NMOSD – Neuromyelitis optica spectrum disorders

IATM – Idiopathic acute transverse myelitis

PI – Post-infectious

ADEM – Acute disseminated encephalomyelitis

SLE – Systemic Lupus Erythematosus

MRI – Magnetic resonance imaging

LETM – Longitudinal extensive transverse myelitis

CSF – Cerebrospinal fluid

IgG – Immunoglobulin G

OCB – Oligoclonal IgG bands

AQP4 – Water channel aquaporin-4

MOG – Myelin oligodendrocyte glycoprotein

VEP – Visual evoked potentials

EDSS – Expanded Disability Status Scale

MSSS – Multiple Sclerosis Severity Score

1. Introduction:

Acute transverse myelitis is an inflammatory SC syndrome (TMCWG, 2002), meaning it presents with motor, sensory and/or autonomic impairment, reflecting SC dysfunction (Beh et al., 2013).
Since this clinical presentation is common to all myelopathies, diagnostic workup should be supported by a detailed history and a complete physical examination and helped by diagnostic imaging and laboratory exams (Beh et al., 2013; Cho and Bhattacharyya, 2018; Greenberg and Frohman, 2015).
According to clinical context, the clinician might perform additional tests, and ruling out treatable causes should be a priority (Cho and Bhattacharyya, 2018; Tobin et al., 2014).
Gathered all information, diagnosis must fit in one of these categories (Zalewski et al., 2018): inflammatory (including demyelinating, infectious and systemic inflammatory diseases), compressive, neoplastic, vascular, toxic or metabolic cause of myelopathy.
Non-infectious inflammatory myelopathies are a common but heterogeneous group of disorders affecting SC (Greenberg and Frohman, 2015). An immune-mediated process is responsible for CNS injuries, which might present with a neurological deficits spectrum, such as myelitis when SC is the region involved (Kaplin et al., 2005).
An accurate diagnose is of great importance, providing to the patient an attempt intervention to prevent further CNS injury and recurrence. Furthermore, it may reduce the long-term burden associated with this event, as well as prevent side effects because of a more selective therapy choice (Greenberg and Frohman, 2015; Yeh and Hintzen, 2018). Therefore, it is important to recognize at presentation those predictors of worse prognosis in order to defeat with stronger therapeutic tools (Greenberg et al., 2019).
Conditions vary on their course, including their tendency to relapse or risk of disability progression, and have specific disease immunological and imaging biomarkers. Descriptive and comparative studies of their characteristics provide to clinicians important clues to their management as well as some security to patients (Debette et al., 2009).

2. Aims:

The aim of our study is to characterize clinical and paraclinical findings of patients admitted to a Portuguese university hospital ward presenting with an acute first non-infectious myelitis episode, and their follow-up. After defining the final diagnosis, we aim to compare characteristics of MS-related myelitis group, including CIS, to those of myelitis of other etiologies. We also intend to recognize features at admission which will allow appropriate distinction and prediction of inflammatory myelitis' neurologic evolution.

3. Material and Methods:

We performed a 10-year's retrospective and descriptive analysis of data gathered prospectively from medical records. We selected adult patients (≥18 years old) admitted for study and treatment to Neurology department ward at Centro Hospitalar Universitário São João (CHUSJ), Portugal, presenting with clinical or imaging SC syndrome compatible findings from 1st January 2007 to 31st December 2016. From these cases, the ones who presented a first episode of acute noninfectious myelitis were included and defined a database.

3.1. Clinical Data:

Clinical and paraclinical data were collected from medical records: gender, age, date of admission, time of symptoms' onset to nadir, neurological exam findings, evidence of previous neurological symptom/disease, family history of neurological disease, supplementary diagnosis tests' results, current diagnosis according to the most recent diagnostic criteria and dysfunction staged by EDSS (Kurtzke, 1983) at admission, discharge and last appointment.

3.2. Definition of cases:

3.2.1. Clinical Presentation:

The patients selected to our database presented sensory (paresthesia, dysesthesia, hypoesthesia, sensory level, Lhermitte's sign), motor (monoparesis, hemiparesis, paraparesis, tetraparesis, impaired walking) and/or autonomic (urinary retention, bowel or bladder incontinence, incomplete evacuation or constipation) symptoms. From symptoms onset to nadir, the time considered compatible with an inflammatory etiology ranged from 4 hours to 21 days, as settled by Transverse Myelitis Consortium Working Group (Schmalstieg and Weinshenker, 2010; TMCWG, 2002).

3.2.2. Etiologies:

Eight etiological subgroups were defined: 1) CIS and 2) MS, defined according to 2017 McDonald criteria (Thompson et al., 2018); 3) IATM, as an exclusion diagnosis and according to Transverse Myelitis Consortium Working Group (TMCWG, 2002) 4) PI myelitis, defined by evidence of recent infection responsible for an autoimmune reaction (Cho and Bhattacharyya, 2018; Kaplin et al., 2005; Schmalstieg and Weinshenker, 2010); 5) NMOSD (Tan et al., 2016); 6) ADEM (Krupp et al., 2007); and 7) other systemic autoimmune diseases with neurological involvement.

3.3. Supplementary diagnosis tests:

3.3.1. Neuroimaging:

Brain and SC MRI were performed in order to identify and measure any inflammatory sign along CNS and their results were reviewed by a neurologist. Brain MRI results were analyzed as Normal or evidence of brain affection, being that these last cases were summarized according to Barkhof criteria (Barkhof et al., 1997): if 3 or more criteria present classified as suggestive of MS. SC MRI, including sagittal and axial planes, were performed and analyzed in order to assess inflammatory signs, such as signal in T2-weighed scans, enhancement by gadolinium contrast and cord swelling. We also registered the number of lesions, their longitudinal extension - according to these subgroups: ≤ 2 segments and > 3 segments, this one there forward defined LETM - and their sagittal (cervical, thoracic, lumbar, sacral, conus medullaris or hollomedullar) and transversal (centromedullary, peripheral, hollocordic and mixed) localization.

3.3.2. CSF and serum analysis:

CSF analysis is a useful diagnostic aid in clinical neurology traducing CNS inflammation, that can be defined by CSF cytology and leucocyte count, considering pleocytosis ≥ 10 total cells/mm^3; IgG index in CSF/serum (> 0,5) and presence of OCB. Serum antibodies are useful tools in this diagnosis workup: anti-AQP4 antibodies and anti-MOG antibodies were detected in serum samples using indirect immunofluorescence techniques, according to a commercial kit (NMOSD Screen 1, EUROIMMUN, Lübeck, Germany).

3.3.3. Additional tests:

VEP is an important tool to assess optic nerve involvement and their results were subdivided into Normal and Increased P100 wave Latencies. In some cases, according to clinical context, additional tests might be requested to exclude secondary etiologies.

3.4. Follow-up:

To characterize each patient follow-up, we decided to take into account the time from diagnosis to last clinical appointment, their most recent EDSS classification and the number of relapses, when applied.

All relapses were identified according to description of new symptoms or signs presented for at least 24 hours, not associated with fever or other medical condition that might unmask subclinical lesions (Inglese, 2006).

We also applied MSSS in all patients to compare disease progression (Roxburgh et al., 2005).

3.5. Exclusion criteria:

Our intention was to describe acute myelitis in adult population, so patients below 18 years were excluded. Findings compatible with compressive, vascular, neoplastic/paraneoplastic, metabolic, infectious and irradiation etiologies were also excluded from the final database (Cho and Bhattacharyya, 2018; Jacob and Weinshenker, 2008; Schmalstieg and Weinshenker, 2010; TMCWG, 2002).

3.6. Statistical analysis:

Data was saved and analyzed using IBM SPSS Statistics V.25. Categorical variables were expressed as percentages. Continuous variables were presented as means with standard deviation, considering their normal distribution by assessing kurtosis values between -1 and 1 and Kolmogorov-Smirnov values > 0,05; or as median and minimum-maximum range, when the permission above described not applied. The different diagnostic groups were compared using ANOVA, Mann-Whitney U, Kruskal-Wallis, chi-square, Fisher's exact test, Bonferroni correction test and *p* values <0,05 were considered of statistical significance. Odds Ratio (OR) was calculated and used as a measure of association.

3.7. Ethical aspects:

The study was approved by Ethics Committee for Health of Centro Hospitalar Universitário São João (CHUSJ), E.P.E, Porto, Portugal.

4. Results

4.1. Population findings and diagnostic etiologies:

A retrospective analysis of inpatient database identified 1327 patients manifesting myelopathy compatible symptoms. Among these, 244 had an acute onset and we selected 71 (29,1%) for presenting a first acute noninfectious inflammatory event (Figure A.1 - *appendices*).
In this myelitis selected group, all individuals were caucasian, 45 (63.4%) were female and 26 (36,6%) were male and were diagnosed with different clinical entities: 7 (9,9%) were diagnosed with CIS, 40 (56,3%) were diagnosed with MS, 9 (12,7%) were diagnosed with NMOSD (4 were NMO seronegative and 4 were NMO seropositive, of 8 patients tested), 8 (11,3%) were diagnosed with IATM, 3 (4,2%) were diagnosed with PI, 2 (2,8%) were diagnosed with ADEM, 2 were

diagnosed with a systemic autoimmune disease with neurological involvement - 1 of them (1,4%) was diagnosed with SLE and the other (1,4%) was diagnosed with Behçet.
Their age at admission ranged from 18 to 80, with a median age of 32 years old. We found statistically significant differences among groups concerning age at presentation (p=0,006).
The onset of symptoms occurred with a median of 7 days, ranging from 2 to 21 days, and there were no statistically significant differences among all etiologies (p=0,440).

4.2. Diagnosis comparisons:

Information concerning clinical presentation, follow-up and demographic data of each diagnostic entity are summarized in Table B.1 - *appendices*.
All symptoms and neurological signs were compared, and a statistically significant difference was assessed to autonomous walking in MS/CIS patients *versus* other groups of diagnosis (p<0,001), as well as for sphincter's related symptoms (p=0,002) and pain (p=0,011) – other comparisons showed no statistically significant differences.
MS/CIS patients showed some specificities, absented on other etiologies, such as positive medical family history in 7 (14,9%) of these patients and 5 (10,6%) MS/CIS patients presented Lhermitte's sign.
When it comes to complementary diagnostic tests, for cranial MRI results there is a statistically significant difference for imaging findings compatible with Barkhof criteria when MS/CIS patients were compared with other diagnosis categories (p<0,001). SC MRI results were also compared: when it comes to longitudinal extension of lesions' subclasses there is also a statistically significant difference between MS/CIS *versus* others (p<0,001); however, there is a trend nearly significant difference between NMOSD *versus* IATM (p=0,05); transversal localization was subcategorized in peripheral lesions and other localizations and no statistically significant difference was observed when comparing MS/CIS *versus* other diagnostics (p=0,374).
Immunological test results were also compared: there is a significant statistic difference concerning OCB positivity when compared all diagnosis (p=0,006); AQP4-antibody positivity showed also statistically significant differences between NMOSD and other diagnoses (p=0,007).
We evaluated EDSS at admission and a statistically significant difference was found between MS/CIS *versus* NMOSD (p=0,001).
Considering follow-up and prognosis variables was found a statically significant difference between MS/CIS *versus* other diagnoses (p=0,004) concerning evidence of relapse, but it did not apply to myelitis relapses. Finally, all MSSS results were also compared and a statistically significant difference was found between MS/CIS *versus* NMOSD (p=0,011).
MS/CIS, IATM, NMOSD were the bigger groups of our cohort of diagnosis, with 47, 8 and 9 patients, respectively. Considering only these 64 patients, the median age at admission was 31

[18-80] years old and there was a statistically significant difference between MS/CIS and NMOSD patients (p=0,001). Overall, a female predominance of 42 (65,6%) women *versus* 22 (34,4%) men cases in all groups persists.

Table 1 – Comparison of MS/CIS, IATM and NMOSD patients.

Characteristics	**MS/CIS n=47**	**IATM n=8**	**NMOSD n=9**	***p* value**
Pain	5 (10,6%)	2 (25,0%)	5 (55,6%)	**0,008**
Autonomous gait	44 (93,6%)	4 (50,0%)	3 (33,3%)	**<0,001**
Sphincter dysfunction	6 (12,8%)	4 (50,0%)	5 (55,6%)	**0,003**
Spinal Cord MRI				
Longitudinal extension				
≤ 2 cord segments	45 (97,8%)*	5 (62,5%)*	1 (11,1%)	
≥ 3 cord segments	1 (2,2%)*	3 (37,5%)*	8 (88,9%)	**<0,001**
Sagittal localization				
Cervical	36 (53,7%)	1 (11,1%)	5 (33,3%)	
Thoracic	30 (44,8%)	7 (77,8%)	9 (60,0%)	-
Conus medullaris	1 (1,5%)	1 (11,1%)	1 (6,7%)	
Transversal localization				
Centromedullary	6 (13,1%)	1 (12,5%)	2 (25,0%)	
Peripheral	30 (65,2%)	6 (75,0%)	2 (25,0%)	
Hollocordic	2 (4,4%)	1 (12,5%)	4 (50,0%)	-
Mixed	8 (17,4%)	0 (0,0%)	0 (0,0%)	
OCB +	35 (74,5%)	2 (25,0%)	3 (33,3%)	**0,004**
Anti-AQP4 +	0 (0,0%)	0 (0,0%)	4 (50,0%)**	**0.024**
Relapses	29 (61,7%)	1 (12.5%)	4 (57,1%)***	**0.039**
Myelitis relapses	17 (58,6%)	1 (100%)	2 (50,0%)	0,478
MSSS >2,5	14 (29,8%)	4 (50,0%)	6 (85,7%)***	**0,015**

Description: The three biggest diagnostic groups were selected and compared. Categorical variables were analyzed using chi-square or Fisher's exact test. Sagittal and transversal localization were defined considering anatomic references and, if present in more than one anatomic segment scored in more than one category. For sagittal and transversal localizations no comparison tests were performed, only descriptive statistics.
Abbreviations: MS: Multiple Sclerosis; CIS: Clinically Isolated Syndrome; IATM: Idiopathic acute transverse myelitis; NMOSD: Neuromyelitis optica spectrum disorders; MRI – Magnetic Resonance Imaging; OCB + : positive oligoclonal bands in cerebrospinal fluid; Anti-AQP4 +: NMO – antibody positivity; MSSS – Multiple Sclerosis Severity Score.
*: one patient from MS/CIS group and IATM group did not show any lesion on spinal cord MRI; **: one patient missed this test; ***: two patients were lost (one died during ward admission and the other was a foreign patient); - : not possible to infer any differences statistically significant considering not all categories have the same representativity.

Table 1 refers to these three groups comparison, concerning clinical presentation, supplementary tests' results and follow-up data.

4.3. Supplementary tests

Table 2 – Comparison among longitudinal extension of cord lesions' categories.

Characteristics	≤ 2 cord segments n=52	≥ 3 cord segments n=16	*p* value
Brain MRI			
Normal	6 (11,5%)	2 (12,5%)	
Non suggestive of MS	9 (17,3%)	12 (75,0%)	**<0,001**
Suggestive of MS	37 (71,2%)	2 (12,5%)	
Spinal cord MRI			
Single lesion	24 (46,2%)	9 (56,3%)	
Multiples lesions	28 (53,8%)	7 (43,7%)	0,572
Sagittal localization			
Cervical	36 (69,2%)	8 (50,0%)	
Thoracic	34 (65,4%)	12 (75,0%)	
Sacral	1 (1,92%)	1 (6,25%)	-
Conus medullaris	2 (3,85%)	1 (6,25%)	
Hollomedullar	0 (0,0%)	2 (12,5%)	
Transversal localization			
Centromedullary	6 (11,5%)	6 (37,5%)	
Mixed	8 (15,4%)	0 (0,0%)	
Peripheral	34 (65,4%)	4 (25,0%)	-
Hollocordic	4 (7,69%)	5 (31,3%)	
EDSS at discharge			
≤2.5	44 (84,6%)	6 (37,5%)	
>2.5	8 (15,4%)	10 (72,5%)	**0,001**
Relapses	30 (57,7%)	4 (28,6%)*	0,073
MSSS >2.5	17 (32,7%)	9 (64,3%)*	0,062

Description: Patients were gathered considering the longitudinal extension of their lesions. Sagittal and transversal localization were defined considering anatomic references and, if present in more than one anatomic segment scored in more than one category.
Categorical variables were compared using chi-square and Fisher's exact test.
Abbreviations: MRI: Magnetic Resonance Imaging; EDSS – Expanded Disability Status Scale; MSSS: Multiple Sclerosis Severity Score; *: two patients were lost follow-up; -: not possible to infer any differences statistically significant considering not all categories have the same representativity.

Table 2 summarizes some clinical and follow-up findings when compared longitudinal extension categories of lesions detected on SC MRI. We observed LETM was associated with higher EDSS at discharge (p=0,001), higher MSSS but lower relapsing rates, even though these two last observations did not show statistically significant differences.

In what concerns immunological tests, anti-AQP4 were positive in 4 of 24 (16,7%) tests requested. Anti-MOG were requested only two times and were both negative – one of the patients was diagnosed with ADEM and the other with NMOSD.

35 patients presented multiple lesions on SC MRI, with a median of 1 lesion detected and a maximum of 9 lesions, and were found statistically significant differences among etiologies (p=0,047). SC MRI did not reveal any lesion in 3 patients, which were diagnosed with different diseases: ADEM, Behçet and MS. Brain MRI was not performed on Behçet's patient.

4.4. Prognosis

69 patients completed follow-up and their follow-up mean time was 52,13 ± 34,87 months. However, 2 out of 71 patients were lost follow-up: one of them died during myelitis event and the second was a foreigner, whose process was transferred to his home country.

34 patients (49,3%) had a relapse of its inflammatory myelopathy etiology and 20 (58,8%) of them had myelitis recurrence. Were found differences statistically significant concerning relapses' number among different etiologies (p=0,013) but it did not apply when compared the number of myelitis relapses (p=0,621). Were found differences statistically significant concerning EDSS at ward's discharge (p<0,001), with highest results attributable to NMOSD and IATM. MSSS results showed, also, highest scores for NMOSD and lowest for SLE and Behçet patients.

19 patients (26,8%) had a full recovery and was found a statistically significant difference when compared the presence of motor symptoms in those who had achieved full recovery and those who had not (p=0,028). Furthermore, we assessed the presence of motor symptoms was associated with a lower rate of full recovery (OR = 0,398 [0,18 – 0,89]).

Table 3 – Clinical and follow-up variables associated with long-term outcome.

Characteristics	MSSS ≤ 2,5 n= 43	MSSS > 2,5 n= 26	*p* value	OR [95% CI]
Age at presentation (years)	27 [18-53]	42,50 [21-68]	**0,005**	
Neurological Previous Symptoms	19 (44,2%)	13 (50,0%)	0,804	
Motor symptoms	18 (41,9%)	23 (88,5%)	**< 0,001**	5,24 [1,74 -15,87]
Sensory symptoms	39 (90,7%)	24 (92,3%)	1,000	
Paresthesias	21 (48,8%)	11 (42,3%)	0,627	
Dysesthesias	18 (41,9%)	5 (19,2%)	0,068	
Hyposthesias	28 (65,1%)	23 (88,5%)	**0,047**	
Sensory level	23 (53,5%)	18 (69,2%)	0,218	

Deep sensory symptoms	14 (32,6%)	12 (46,2%)	0,31	
Bilateral symptoms	23 (53,5%)	17 (65,4%)	0,451	
Pyramidal tract symptoms	15 (65,4%)	15 (25,0%)	0,082	
Walking impairment	3 (7,0 %)	11 (42,3%)	**0,001**	2,88 [1,73 – 4,80]
Autonomic symptoms	10 (23,3%)	10 (38,5%)	0,273	
Pain	6 (14,0%)	8 (30,8%)	0,125	
EDSS at onset	2,50 [0-7]	4,00 [2-8,5]	**0,009**	
EDSS at discharge	1,50 ±1,31	3,19±1,71	**<0,001**	
Relapses	18 (41,9%)	16 (61,5%)	0,140	
Myelitis relapses	9 (20,9%)	11 (42,3%)	0,099	1,80 [1,01 – 3,21]

Description: Patients were gathered considering their MSSS category: MSSS ≤ 2,5 or MSSS > 2,5. We evaluated all continuous variables in order to assess their normal distribution or not, and EDSS at discharge was the one who showed a normal distribution considering both criteria. Meanwhile, age at admission only obeyed to kurtosis assumption. All continuous variables that did not show a normal distribution were described using median and minimum-maximum range and were analyzed using non-parametric tests to compare median results. All continuous variables that did show a normal distribution were described using mean and standard deviation and were compared using ANOVA tests and Levene's test to assure equal variances. Categorical variables were compared using chi-square or Fisher's exact test.
Risk of having MSSS > 2,5 when certain finding at admission/registered in follow-up data was presented was calculated using Odds Ratio (OR) and respective 95% confidence interval (95% CI) when proved association.
Abbreviations: EDSS – Expanded Disability Status Scale; MSSS: Multiple Sclerosis Severity Score; *: two patients were lost follow-up.

26 (37,7%) presented MSSS above 2,5 at the last medical appointment recorded and Table 3 summarizes symptoms presented at admission, follow-up data and their prognosis on long-term, represented by MSSS classes.

5. Discussion

Diagnosis categories were established according to most recent criteria and, when appropriated, reconsidered according to most updated data at the time.

MS is the most well recognized demyelinating disease and, therefore, the most studied and in 2017 new McDonald MS diagnostic criteria were published (Carroll, 2018).

Our MS/CIS patients presented a female predominance and median age lower than other etiologies, reflecting a predominant affection of adults in their 3^{rd} – 4^{th} decade of life. These findings are compatible with demographic characterization in the literature (Raffel et al., 2016).

Sensory symptoms were more prevalent than motor ones, with a high prevalence of cases with autonomous gait preserved. Pain is relatively uncommon in these patients as well as autonomic impairment, as observed. Lhermitte's sign reflects a demyelinating lesion of SC posterior columns and is frequently associated with MS, which is consistent with our study - only MS/CIS patients presented Lhermitte's sign.

As expectable, brain MRI had typical findings considered in Barhkof criteria and 26.3% presented increased latencies, reflecting optical nerve involvement as a possible lesion in MS.

OCB positivity is also an important marker, contemplated in new McDonald MS diagnostic criteria, and the majority of patients presented it in CSF tests, as well as an increased IgG index (McNicholas et al., 2018). Pleocytosis, another marker of CNS inflammation, was not present in the majority of MS/CIS, which is consistent with the literature (Gastaldi et al., 2017; Wingerchuk, 2018).

As observed in our study, lesions are usually small in extension (less than 3 vertebral segments) and have a peripheral transversal localization (Jacob and Weinshenker, 2008).

Even though only 17,5% reached complete recovery, MS presented lower EDSS and MSSS than other relapsing etiologies.

NMOSD, out of all etiologies studied, it was the one with a higher median age at presentation and MSSS, as well as a lower recovery rate.

The increased latencies on VEP are compatible with well recognized optic neuritis that names this disorders group.

On MRI, as expected, majority presented LETM and even though none had a normal cranial MRI, vast majority did not obey Barkhof criteria, reflecting a different affection of CNS than MS/CIS (Jurynczyk et al., 2015). Anti-AQP4 is a classic immunologic marker of NMOSD and was only positive in 4 of 8 patients tested. However, it is known some patients presenting typical phenotype of NMOSD are anti-AQP4 seronegative, and it has been suggested that these patients should be tested for anti-MOG (de Seze, 2017; Jurynczyk et al., 2017; Zamvil and Slavin, 2015). Anti-MOG is neither a stable nor a specific immunological marker for NMOSD and is described in many other neurologic disorders, such as ADEM (de Seze, 2017). It has also been described anti-MOG NMOSD phenotype differs from anti-AQP4 NMOSD, concerning clinical and prognostic features (Kitley et al., 2014), and double positivity is not usually seen, suggesting distinct pathological mechanisms (Dos Passos et al., 2018). In our study, only two patients were tested for anti-MOG antibody, none of them were positive and only one was diagnosed with anti-AQP4 seronegative NMOSD. We believe this low rate of anti-MOG assessment happened because of the retrospective design and timeline of our study since anti-MOG seropositive NMOSD is a recent and emergent entity (Mader et al., 2011).

ADEM is also a well-known inflammatory demyelinating disorder of CNS in pediatric age rather rarer in adult population. It traditionally presents as a monophasic condition, compatible with our no-relapses findings, and brain MRI usually shows multiple white matter lesions that do not obey Barkhof criteria, also compatible with our results (Wingerchuk and Weinshenker, 2013). It is a differential diagnosis for LETM and typically presents with bilateral symptoms, all these characteristics described in the literature are also consistent with our findings. Immunology tests,

such as OCB and anti-AQP4, were all negative as expected (Wingerchuk and Weinshenker, 2013), as well as anti-MOG in the patient tested.

Recent developments in neuroimaging, as well as the discovery of specific neuroinflammatory biomarkers, have been responsible to identify and come to a diagnostic conclusion about patients who, otherwise, would have an idiopathic condition diagnosed (Yeh and Hintzen, 2018). IATM criteria were published before the last years' advances in diagnostic tools and not reviewed after that (Yeh and Hintzen, 2018; Zalewski et al., 2018). Besides that, IATM was one of the three bigger diagnostic groups.

SLE and Behçet's Disease (Lukjanowicz and Brzosko, 2009; Piquet and Clardy, 2018; Yu et al., 2014) are both systemic diseases with neurological affection but not two classic diagnoses for myelitis. In our study, we had a very small sample of systemic diseases as a cause of myelitis, which makes it harder to come up with some conclusions. Furthermore, these two patients did not complete all diagnosis workup: they were not tested for anti-AQP4, which might be important since some SLE patients have coexisting NMOSD (Kim et al., 2017), OCB status was not assessed and did not complete MRI study.

ADEM, NMOSD, PI and SLE were the etiologies with higher rates of LETM, an imaging entity typically associated with higher disability grades (Wingerchuk and Weinshenker, 2013), as observed in our study. In 3 cases, no lesion was identified on SC MRI, which was presumed to be a consequence of MRI image obtained in a too short period of time.

Long-term prognosis was analyzed in order to come up with some conclusions about prognostic predictors at admission that might guide clinicians to prevent further impairment. As observed, the presence of motor symptoms predicts a worse prognosis (OR = 5,24 [1,74 – 15,87]), as well as the absence of autonomous walking (OR=2,88 [1,73 – 4,80]), but no association was found in what concerns autonomic dysfunction. We found statistically significant differences concerning EDSS at admission and at discharge when comparing MSSS above *vs* equal or below 2,5, but it did not apply to relapses. Therefore, we may conclude that impairment at admission and at discharge are truly important long-term conditioners to functional capacity, so an effective approach is of essential importance to reduce this burden (Greenberg et al., 2019). Time delay to get a diagnosis or number of wrong diagnosis were not assessed but it is intuitive that this might contribute to a worse outcome for these patients, especially those with a relapsing course of disease.

We believe not considering therapeutic approach is an important limitation of our study because many of these demyelinating diseases already have modifying prognosis therapy, which might have an impact in prognosis outcomes, as evaluated through relapses and MSSS variables.

Also, the retrospective design of this study made it impossible to assure a uniform approach, in what concerns all diagnostic workup and data collected from medical records. Another limitation that impaired our ability to achieve some conclusions was the small group representation of non-

MS/CIS diagnosis, which might be overcome if performed a prospective national database study so that we can have a greater representation of non-MS/CIS cases.
We used MSSS in order to obtain information about disability progression over time, avoiding time as a confounder, in all these patients. However, we are aware of this scale was not validated for other diseases besides MS, which have different disease mechanisms as well as a different course.
Despite that, we believe our study has accomplished its main aims and even though this is a small sample, it resembles findings validated in the most recent literature.

6. Conclusion

Noninfectious inflammatory myelopathies have heterogeneous courses but present overlapping features (Wingerchuk, 2018).
No single feature is enough to define a disorder with absolute certainty and diagnostic workup of SC inflammatory processes should be no strict but rather broaden, reflecting clinical context to look after a proper diagnosis, and time saver to exclude other reversible differential diagnoses (Greenberg and Frohman, 2015; Stangel et al., 2013). While SC MRI is the gold standard imaging technique (Greenberg and Frohman, 2015), brain MRI and CSF analysis are essential tools that complement all information about CNS affection (Cho and Bhattacharyya, 2018). As in everything in medicine, diagnosis is a probabilistic game where all information gathered help us go through clinical thinking.
A proper diagnosis is critical to assess effective and targeted therapy, so we can reduce the burden of adverse effects and estimate patients' prognosis, considering relapsing and impairment features (Greenberg and Frohman, 2015; Wingerchuk, 2018).

7. Conflict of interests: None.

8. Financial disclosure: The authors have nothing to disclose.

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Anexos

I. Normas de Publicação da Revista *Multiple Sclerosis and Related Disorders*

II. Parecer e autorização da Comissão de Ética do Centro Hospitalar Universitário São João, E.P.E, Porto, PORTUGAL, para a realização da investigação

MULTIPLE SCLEROSIS AND RELATED DISORDERS

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DESCRIPTION

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Please click here for the checklist and the complete article by Sandra Amor and David Baker.

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AFTER ACCEPTANCE

Availability of accepted article
This journal makes articles available online as soon as possible after acceptance. This concerns the accepted article (both in HTML and PDF format), which has not yet been copyedited, typeset or proofread. A Digital Object Identifier (DOI) is allocated, thereby making it fully citable and searchable by title, author name(s) and the full text. The article's PDF also carries a disclaimer stating that it is an unedited article. Subsequent production stages will simply replace this version.

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Unidade de Investigação

Tomei conhecimento. Nada a opor.

30 de Outubro de 2018

A Coordenadora da Unidade de Investigação

(Prof.ª Doutora Ana Azevedo)

DIRECÇÃO CLÍNICA

Aprovado. Ao CA. 2 / 11 / 2018

(Prof.ª Doutora Ana Azevedo)

n.º 240 / 18

SÃO JOÃO

PEDIDO DE AUTORIZAÇÃO

Realização de Investigação

Exmo. Senhor Presidente do Conselho de Administração
do Centro Hospitalar de São João

AUTORIZADO

CONSELHO DE ADMINISTRAÇÃO REUNIÃO DE 08 NOV 2018

Presidente do Conselho de Administração

(Dr. António Oliveira e Silva)

Diretor Clínico | Enfermeira Diretora | Vogal Executivo | Vogal Executivo

(Prof. Dr. José Artur Paiva) | (Enf.ª Filomena Cardoso) | (Dr. Luís Porto Gomes) | (Dr. Roberto G. Matos)

Nome do Investigador Principal:

Ana Filipa Santos Martins

Título da Investigação:

Revisão de Mielites Inflamatórias em 10 anos num Serviço Hospitalar de Neurologia

Pretendendo realizar no(s) Serviço(s) de:

Neurologia

a investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efetivação.

Para o efeito, anexo toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de São João/ Faculdade de Medicina da Universidade do Porto respeitante à investigação, à qual enderecei pedido de apreciação e parecer.

Com os melhores cumprimentos.

O Investigador/ Promotor

Porto, 3 *de* agosto *de* 2018 .

Ana Filipa Santos Martins
assinatura

Centro de Investigação HSJ
RECEBI
3 / 10 / 2018

SÃO JOÃO
Documento para Reunião de CA
Rececionado
02 NOV 2018

CES-IM005-0

Parecer da Comissão de Ética para a Saúde do
Centro Hospitalar de São João / Faculdade de Medicina da Universidade do Porto

Título do Projeto: Revisão de Mielites Inflamatórias em 10 anos num Serviço Hospitalar de Neurologia

Nome da Investigadora Principal: Ana Filipa Santos Martins, estudante do Mestrado Integrado em Medicina da FMUP

Onde decorre o Estudo: No Serviço de Neurologia do CHSJ. Dispõe de autorização da Prof.ª Doutora Elsa Azevedo. O profissional de ligação será o Dr. Luís Carlos Pereira Braz.

Objetivos do Estudo:
Revisão de casos de mielite inflamatória não infeciosa internados/seguidos no Serviço de Neurologia do Centro Hospital São João em 10 anos:

- Elaboração de base de dados que inclua todos os casos com quadro clínico de mielopatia internados no S. Neurologia do CHSJ, o seu diagnóstico final e dados clínicos e paraclínicos (ECD, tratamento, seguimento/evolução);
- Revisão dos diagnósticos finais dos casos de mielite inflamatória face às classificações mais recentes;
- Avaliação estatística da informação recolhida e correlação com os diferentes diagnósticos etiológicos;
- Discussão do impacto da evidência obtida.

Insere-se no âmbito do Mestrado Integrado em Medicina da FMUP, sob orientação da Prof.ª Doutora Joana Guimarães e co-orientação do Dr. Luís Carlos Pereira Braz.

Conceção e Pertinência do estudo:
As mielopatias constituem um grupo bastante heterogéneo de doenças que afetam a medula espinal e cujas principais manifestações são insuficientes para esclarecer a sua etiologia.
As mielites inflamatórias são um subgrupo de mielopatias, de causa inflamatória não infeciosa, podendo ser, do ponto de vista etiológico, secundárias a várias patologias (das quais a EM é a mais comum) ou idiopáticas.
Ainda que a abordagem inicial mais frequente seja a corticoterapia em alta dose, o conhecimento cada vez mais profundo da patofisiologia de cada condição secundária permite abordagens terapêuticas mais direcionadas, bem como um seguimento adequado às necessidades, que resulte num melhor *outcome*.

Será realizada uma revisão de 10 anos de todos os casos de mielopatias não infeciosas identificadas, internados no S. Neurologia do CHSJ, no período de 1 de janeiro de 2007 a 31 de dezembro de 2016.
Com a informação recolhida será feito um estudo estatístico no sentido de perceber a prevalência relativa de cada etiologia e repercussões no seguimento e *outcome* a longo prazo.

Benefício/risco: Não aplicável

Confidencialidade dos dados: a anonimização da informação recolhida será assegurada através de números de identificação (Id) atribuídos aos doentes, sendo que apenas os investigadores responsáveis saberão a correspondência.

Respeito pela liberdade e autonomia do sujeito de ensaio: Não aplicável

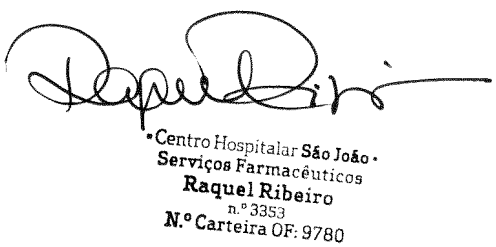
***Curriculum* da investigadora**: Adequado à investigação.

Data previsível da conclusão do estudo: Março de 2019

Conclusão: Face ao exposto, proponho um parecer favorável à realização deste projecto de investigação.

Porto, 21 de Setembro de 2018

O Relator da CES,



SÃO JOÃO

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FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

Questionário para submissão de Investigação

Exmo. Sr. Presidente da Comissão de Ética do Centro Hospitalar de São João/ Faculdade de Medicina da Universidade do Porto,

Pretendendo realizar a investigação infracitada, solicito a V. Exa., na qualidade de Investigador, a sua apreciação e a elaboração do respetivo parecer. Para o efeito, anexo toda a documentação requerida.

IDENTIFICAÇÃO DO ESTUDO

Título da investigação: Revisão de Mielites Inflamatórias em 10 anos num Serviço Hospitalar de Neurologia

Nome do investigador: Ana Filipa Santos Martins

Endereço eletrónico: afilipam21@gmail.com **Contacto telefónico:** 916458463

Caracterização da investigação:

☒ Estudo retrospetivo ☒ Estudo observacional ☐ Estudo prospetivo

☐ Inquérito ☐ Outro. Qual? _____

Tipo de investigação:

☐ Com intervenção ☒ Sem intervenção

Formação do investigador em boas práticas clínicas *(GCP)*: ☐ Sim ☒ Não

Promotor *(se aplicável)*: _____

Nome do orientador de dissertação/tese *(se aplicável)*: Joana Cruz Guimarães Ferreira Almeida

Endereço eletrónico: joanaalmeida@med.up.pt

Local/locais onde se realiza a investigação: Serviço de Neurologia do CHSJ

Data prevista para início: _____/_____/_____ Data prevista para o término: _____/_____/_____

PROTOCOLO DO ESTUDO

Síntese dos objetivos:

Revisão de casos de mielite inflamatória não infeciosa internados/seguidos no Serviço de Neurologia do Centro Hospital São João nos últimos 10 anos.
Estabelecimento de correlação entre dados clínicos e paraclínicos (à admissão e no seguimento) e os diferentes diagnósticos etiológicos.

Fundamentação ética (ganhos em conhecimento/inovação; ponderação benefícios/riscos):

Reconhecimento de características associadas às diferentes etiologias das mielites inflamatórias não infeciosas.

CONFIDENCIALIDADE

De que forma é garantida a anonimização dos dados recolhidos de toda a informação?

O investigador necessita ter acesso a dados do processo clínico? ☒ Sim ☐ Não

Está previsto o registo de imagem ou som dos participantes? ☐ Sim ☒ Não

Se sim, está prevista a destruição deste registo após o sua utilização? ☐ Sim ☐ Não

CONSENTI MENTO

O estudo implica recrutamento de:

Doentes: ☐ Sim ☒ Não Voluntários saudáveis: ☐ Sim ☒ Não

Menores de 18 anos: ☐ Sim ☒ Não

Outras pessoas sem capacidade do exercício de autonomia: ☐ Sim ☒ Não

A investigação prevê a obtenção de Consentimento Informado: ☐ Sim ☒ Não

Se não, referir qual o fundamento para a isenção:

Análise retrospetiva de processos clínicos, sem intervenção.

Existe informação escrita aos participantes: ☐ Sim ☒ Não

PROPRIEDADE DOS DADOS

A investigação e os seus resultados são propriedade intelectual de:

☒ Investigador ☐ Promotor ☐ Ambos ☒ Serviço onde é realizado

☐ Não aplicável Outro: _____

BENEFÍCIOS, RISCOS E CONTRAPARTIDAS PARA OS PARTICIPANTES

Benefícios previsíveis:

Melhor conhecimento dos diagnósticos etiológicos desta patologia.

Riscos/incómodos previsíveis:

São dadas contrapartidas aos participantes:

- *pela participação* ☐ Sim ☐ Não ☐ Não aplicável
- *pelas deslocações* ☐ Sim ☐ Não ☐ Não aplicável
- *pelas faltas ao emprego* ☐ Sim ☐ Não ☐ Não aplicável
- *por outras perdas e danos* ☐ Sim ☐ Não ☐ Não aplicável

CUSTOS / PLANO FINANCEIRO

Os custos da investigação são suportados por:

☐ Investigador ☐ Promotor ☐ Serviço onde é realizado

☒ Não aplicável Outro: _____

Existe protocolo financeiro? ☐ Sim ☒ Não

LISTA DE DOCUMENTOS ANEXOS

- [x] Pedido de autorização ao Presidente do Conselho de Administração do Centro Hospitalar de São João *(se aplicável)*
- [ ] Pedido de autorização à Diretora da Faculdade de Medicina da Universidade do Porto *(se aplicável)*
- [x] Protocolo do estudo
- [x] Declaração do Diretor de Serviço onde decorre o estudo
  (sendo um estudo na área de enfermagem deve anexar também a concordância da chefia de enfermagem)
- [x] Profissional de ligação
- [x] Informação dos orientadores
- [ ] Informação ao participante
- [ ] Modelo de consentimento
- [ ] Instrumentos a utilizar *(inquéritos, questionários,escalas, p.ex.)*: _____
- [x] Curriculum Vitae abreviado *(máx. 3 páginas)*
- [ ] Protocolo financeiro
- [ ] Outros:

COMPROMISSO DE HONRA E DECLARAÇÃO DE INTERESSES

Declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (1960 e respetivas emendas), e da Organização Mundial da Saúde, Convenção de Oviedo e das "Boas Práticas Clínicas" (GCP/ICH) no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo, nos últimos três meses. Comprometo-me a entregar à CES o relatório final da investigação, assim que concluído.

Porto, 3 *de* agosto *de* 2018

Nome legível: Ana Filipa Santos Martins

Ana Filipa Santos Martins
assinatura

Parecer da Comissão de Ética do Centro Hospitalar de São João/ FMUP Emitido na reunião plenária da CE de 14 / 09 / 18

A Comissão de Ética para a Saúde tendo aprovado o parecer do Relator, aguarda que o Investigador/Promotor esclareça as questões nele enunciadas para que possa emitir parecer definitivo.

Centro Hospitalar **São João**

CONSIDERADOS QUE FORAM COMO SATISFATÓRIOS OS ESCLARECIMENTOS PRESTADOS PELO(A) INVESTIGADOR(A), A CES APROVA POR UNANIMIDADE O PARECER DO RELATOR, PELO QUE NADA TEM A OPOR À REALIZAÇÃO DESTE PROJETO DE INVESTIGAÇÃO.

25/09/18

240-18

RESPONSÁVEL PELO ACESSO À INFORMAÇÃO

SÃO JOÃO

Pedido de Reutilização de Registos Clínicos para Investigação e Desenvolvimento (I&D)

Número do Pedido
118101212104591
(A preencher pelo Gabinete de Apoio ao RAI)

Exmo Senhor
Responsável pelo Acesso à Informação
(Artigo 9º da Lei nº 26/2016 de 22 de agosto)
Dr. Rui de Vasconcellos Guimarães

AUTORIZADO
RAI Responsável pelo Acesso à Informação no Centro Hospitalar de São João
(Artigo 9º, Lei 26/2016, de 22/8)
VASCONCELLOS GUIMARÃES
Administrador Hospitalar
2 / 10 / 2018

1. Identificação do(s) Investigador(es) *Preenchimento Obrigatório*

1.1. Investigador Principal
Nome Ana Filipa Santos Martins
Contacto telefónico +|3|5|1|9|1|6|4|5|8|4|6|3|
Endereço eletrónico afilipam21 @ gmail.com

1.2. Investigador(es) Associado(s)
Número Total: 2
Nome Joana Cruz Guimarães Ferreira Almeida
Contacto telefónico +|3|5|1|9|1|2|4|2|8|5|6|3|
Endereço eletrónico joanaalmeida @ med.up.pt

Nome Luís Carlos Pereira Braz
Contacto telefónico +|3|5|1|9|1|6|7|0|0|7|8|7|
Endereço eletrónico luispereirabraz @ gmail.com

Nome
Contacto telefónico
Endereço eletrónico @

1.3. Afiliação Institucional do Investigador Principal
1.3.1. Grupo Profissional
☐ Médico(a) ☐ Enfermeiro(a) ☐ Docente ☒ Estudante
☐ Outro. Qual?

1.3.2. Documento de identificação pessoal ou profissional
☐ Cartão de Cidadão ☒ Bilhete de Identidade ☐ Célula Profissional
☐ Cartão de Docente ☐ Cartão de Estudante ☐ Outro. Qual?
Número de Documento 1|4|9|1|4|4|4|3|

2. Enquadramento e Identificação do Trabalho de Investigação e Desenvolvimento *Preenchimento Obrigatório*

2.1. Enquadramento da investigação
☒ Trabalho académico de investigação e desenvolvimento:
☐ Não conferidor de grau
☒ Conferidor de grau: ☐ Licenciatura ☒ Mestrado ☐ Doutoramento
☐ Projeto de investigação e desenvolvimento

2.2. Entidade(s) que tutela(m) a investigação

☒ Centro Hospitalar de São João

Serviço: de Neurologia

☒ Universidade do Porto

Faculdade / Instituto: Faculdade de Medicina da Universidade do Porto

☐ Outra Instituição. *Qual?*

Há alguma parceria entre instituições?

☒ Não ☐ Sim. Qual(is)?

2.3. Orientador Se Aplicável

Contacto telefónico | + | 3 | 5 | 1 | 9 | 1 | 2 | 4 | 2 | 8 | 5 | 6 | 3 |

Endereço eletrónico joanaalmeida @ med.up.pt

2.4. Título provisório

Revisão de Mielites Inflamatórias em 10 anos num Serviço Hospitalar de Neurologia

Deverá posteriormente indicar o título definitivo para emissão do Certificado de Reutilização pelo RAI - DAta REuse Certificate for Research - DARE através dos contactos disponíveis no fim deste formulário.

2.5. Acesso requerido

☐ Ficheiro

Descrição do património informacional a que pretende ter acesso, identificando a informação a obter, i.e. nome, morada, diagnóstico, idade, códigos dos distritos, entre outros.

☐ Consulta de processos clínicos em ambiente papel:

☐ Bloco ☐ Consulta Externa ☐ Hospital de Dia ☐ Internamento ☐ MCDT ☐ Urgência

Deverá anexar ficheiro(s) contendo a identificação do pretendido, i.e. números de processos, episódios, números de utente, entre outros.

Anexar ficheiro(s) ao pedido online

☒ Consulta de registos clínicos eletrónicos

Especificar os Sistemas de Informação:

SClínico

Data previsível de fim de utilização das credenciais de acesso | 2 | 0 | 1 | 8 | - | 1 | 2 | - | 3 | 1 |

☐ Outro Acesso. Qual?

2.3. Pareceres e Autorizações

☒ Autorização da Hierarquia

☒ Protocolo Científico Aprovado [1]

☒ Parecer da Comissão de Ética para a Saúde (CES) [1]

☐ Parecer do Centro de Epidemiologia Hospitalar [1]

Deverá anexar ficheiro(s) contendo cópia dos documentos referentes às opções selecionadas.

Anexar ficheiro(s) ao pedido online

[1] Obrigatório quando aplicável

3. Observações *Preenchimento Facultativo*

4. Aceitação dos Termos e Condições da Reutilização

Cumulativamente com as obrigações decorrentes da lei já citada *(n.º 2 e 3 do artigo 21 e o n.º 1 e 2 do artigo 12, ambos da Lei n.º 26/2016, de 22 de agosto)* ao submeter o presente pedido concordo e fico ainda vinculado aos seguintes termos e condições:

- Comprometo-me a manter confidencial toda a informação à qual vou ter acesso;
- Não vou elaborar registos, susceptíveis de identificar ou tornar identificável a identidade das pessoas a quem os mesmos dizem respeito;
- Não vou elaborar, nem ficar na posse, de cópias de bases de dados utilizadas na recolha de informação;
- Comprometo-me a obter junto da Comissão Nacional de Proteção de Dados (CNPD) as necessárias autorizações, para eventuais bases de dados que venha a conceber e utilizar no âmbito da presente investigação;
- Comprometo-me a devolver ao Centro Hospitalar de São João, na pessoa do seu Diretor Clínico, as bases de dados e o resultado da investigação;
- Comprometo-me a ocultar os elementos de identificação da(s) pessoa(s) a quem os registos digam respeito, em futuras e eventuais publicações de resultados;
- Comprometo-me a consultar os processos clínicos nas instalações que me forem indicadas para o efeito;
- Comprometo-me a obter os necessários pareceres, quer da Comissão de Ética do Hospital, quer do Centro de Epidemiologia Hospitalar, sempre que necessário;
- Comprometo-me a citar as fontes sempre que publicitar o trabalho de investigação independentemente de requerer a Certidão de Reutilização (DAta REuse Certificate for Research – DARE);
- Tomei conhecimento, que a violação de qualquer dos compromissos aqui assumidos, resultará no apuramento de responsabilidades disciplinares, civis e penais e ainda, à impossibilidade futura de aceder a informação de saúde para fins de investigação.

5. Decisão do investigador sobre requerer a DAta REuse Certificate for Research – DARE *Preenchimento Obrigatório*

☒ Pretendo desde já requerer a Certidão de Reutilização (DARE) cujo sentido, valor e significado consultei em *http://portal-chsj.min-saude.pt/pages/710*.

☐ Não pretendo requerer a Certidão de Reutilização (DARE) cujo sentido, valor e significado consultei em *http://portal-chsj.min-saude.pt/pages/710*.

6. Assinatura

Nota 1: Se o presente pedido for submetido eletronicamente ou faz assinatura digital qualificada; ou posteriormente vem ao Centro Hospitalar de São João exibir o seu documento de identificação pessoal, ou no âmbito do seu espaço de liberdade e como manifestação expressa do seu consentimento envio cópia do referido documento, neste caso, concluído o processo será-lhe devolvida ou eliminada a cópia do documento de identificação pessoal, conforme as indicações que dê.
Nota 2: Se o presente pedido for entregue presencialmente, assina e exibe o documento de identificação a quem recebe o pedido.

Data 2018-09-27

Ana Filipa Santos Martins
Investigador Principal

Em caso de dúvida no preenchimento contacte através dos endereços eletrónicos
rai.reutilizacao.id@chsj.min-saude.pt **ou** ruiguimaraes@chsj.min-saude.pt
ou pelos números de telemóvel 962 204 194 **ou** 918 880 299

SUBMETER

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UNIVERSIDADE DO PORTO

Apêndices

Appendices

A. Figures

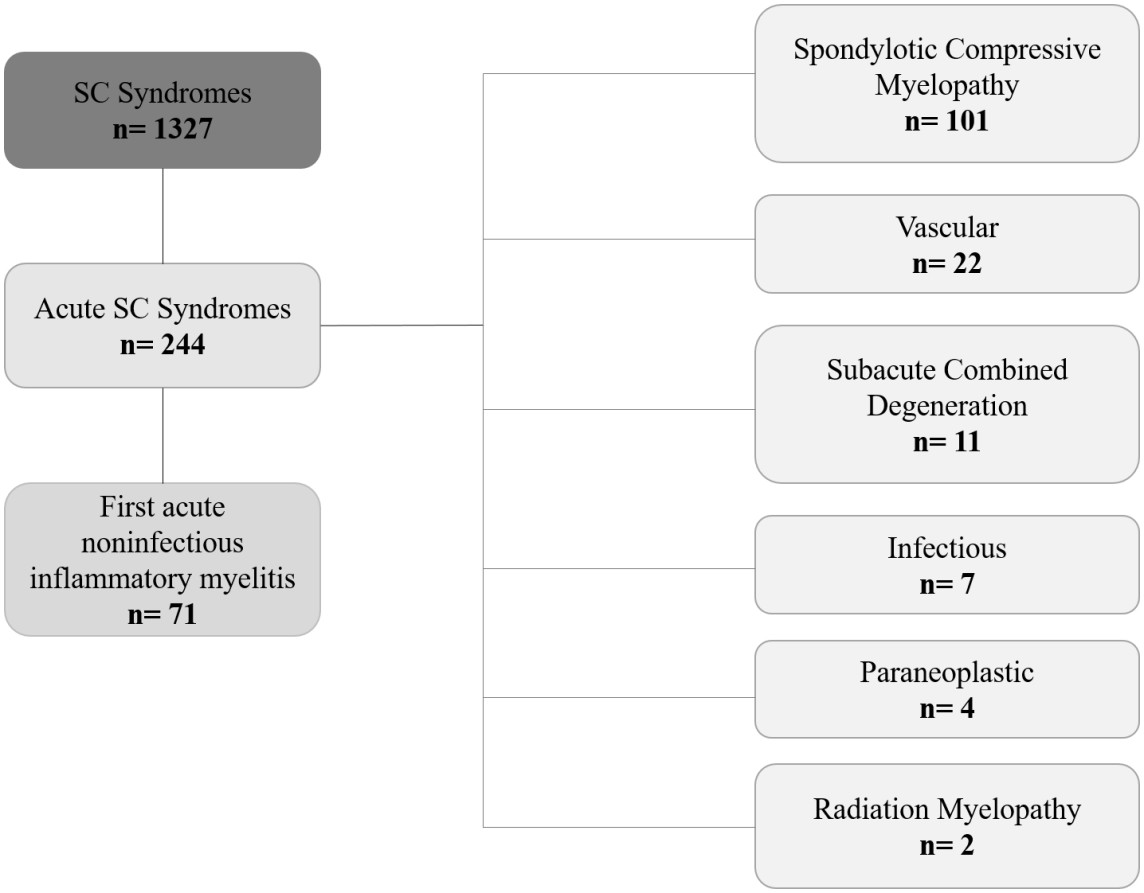

Figure A.1- Diagram showing SC syndromes identified and those included and excluded from the study, considering their onset and etiology.

Description: Considering all admissions to the Department of Neurology of CHUSJ from 1st January of 2007 to 31st December of 2016, 1327 patients presented a SC Syndrome. 244 patients were selected for having an acute manifestation, 147 of these were diagnosed with a secondary cause of their myelopathy. From the others, 71 patients were carefully chosen and constituted our final database considering only first acute noninfectious inflammatory myelitis.
Abbreviations: SC: Spinal Cord

B. Tables

Table B.1 – Clinical, paraclinical and follow-up characteristics of the study subjects according to etiologic diagnosis.

Characteristics	MS n=40	CIS n=7	ADEM n=2	NMOSD n=9	IATM n=8	PI n=3	SLE n=1	BEHÇET n=1	Total n=71	*p* value
Gender (F:M)	29:11	4:3	1:1	5:4	4:4	0:3	1:0	1:0	45:26	0,259
Age at onset (years)	27,5 [18-68]	23 [19-29]	36 [33-39]	56 [27-80]	36,5 [21-54]	44 [20-53]	36	47	32 [18-80]	**0,006**
Time of onset (days)	7 [2-21]	7 [5-14]	13,5 [10-17]	11 [1-21]	8 [1-14]	5 [3-18]	3	4	7 [1-21]	0,440
Neurological previous symptoms	24 (60,0%)	2 (28,6%)	1 (50,0%)	2 (22,2%)	3 (37,5%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	32 (45,1%)	0,158
Motor symptoms	23 (57,5%)	4 (57,2%)	1 (50,0%)	9 (100%)	3 (37,5%)	2 (66,7%)	1 (100%)	0 (0,0%)	43 (60,6%)	0,180
Monoparesis	8 (20,0%)	2 (28,6%)	0 (0,0%)	1 (11,1%)	1 (12,5%)	0 (0,0%)	0 (0,0%)	-	12 (16,9%)	0,650
Paraparesis	3 (7,5%)	1 (14,3%)	1 (50,0%)	3 (33,3%)	2 (25,0%)	2 (66,7%)	1 (100%)	-	13 (18,3%)	
Hemiparesis	5 (12,5%)	1 (14,3%)	0 (0,0%)	2 (22,3%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	-	8 (11,3%)	
Triparesis	3 (7,5%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	-	3 (4,2%)	
Tetraparesis	4 (10,0%)	0 (0,0%)	0 (0,0%)	3 (33,3%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	-	7 (9,9%)	
Hyperreflexia	19 (47,5%)	5 (71,4%)	0 (0,0%)	4 (44,4%)	1 (12,5%)	1 (33,3%)	1 (100%)	0 (0,0%)	31 (43,7%)	0,229
Sensory symptoms	37 (92,5%)	6 (85,7%)	1 (50,0%)	9 (100%)	8 (100%)	2 (66,7%)	1 (100%)	1 (100%)	65 (91,5%)	0,255
Paresthesias	19 (47,5%)	3 (42,9%)	0 (0,0%)	4 (44,4%)	5 (62,5%)	1 (33,3%)	1 (100%)	0 (0,0%)	33 (46,5%)	0,677
Dysesthesias	14 (35,0%)	1 (14,3%)	1 (50,0%)	4 (44,4%)	3 (37,5%)	0 (0,0%)	0 (0,0%)	1 (100%)	24 (33,8%)	0,545
Hyposthesias	31 (77,5%)	5 (71,4%)	1 (50,0%)	8 (88,9%)	4 (50,0%)	2 (66,7%)	0 (0,0%)	1 (100%)	52 (73,2%)	0,385

Sensory level	22 (55,0%)	4 (57,1%)	1 (50,0%)	7 (77,8%)	6 (75,0%)	0 (0,0%)	1 (100%)	1 (100%)	42 (59,2%)	0,314
Deep sensory symptoms	13 (32,5%)	1 (14,3%)	1 (50,0%)	6 (66,7%)	5 (62,5%)	1 (33,3%)	0 (0,0%)	0 (0,0%)	27 (38,0%)	0,272
Bilateral symptoms	17 (42,5%)	4 (57,1%)	2 (100%)	8 (88,9%)	6 (75,0%)	3 (100%)	1 (100%)	1 (100%)	42 (59,2%)	0,06
Pyramidal tract symptoms	16 (40,0%)	4 (57,1%)	0 (0,0%)	7 (77,8%)	1 (12,5%)	2 (66,7%)	1 (100%)	0 (0,0%)	31 (43,7%)	0,088
Autonomous gait	38 (95,0%)	6 (85,7%)	1 (50,0%)	3 (33,3%)	4 (50,0%)	2 (66,7%)	0 (0,0%)	1 (100%)	55 (77,5%)	**0,001**
Autonomic symptoms	4 (10,0%)	2 (28,6%)	2 (100%)	5 (55,6%)	4 (50,0%)	3 (100%)	1 (100%)	0 (0,0%)	21 (29,6%)	**<0,001**
Pain	5 (12,5%)	0 (0,0%)	1 (50,0%)	5 (55,6%)	2 (25,0%)	1 (33,3%)	0 (0,0%)	0 (0,0%)	14 (19,7%)	0,086
EDSS at onset	2,5 [0-7]	2 [1-4,5]	3 [3-3]	6 [2,5-9]	4,5 [1-8]	7 [1-7]	2,5	2	3 [0-9]	0,094
Spinal Cord MRI										
Multiple Lesions	24 (60,0%)	4 (57,1%)	0 (0,0%)	6 (66,7%)	1 (12,5%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	35 (50,0%)	**0,033**
Longitudinal extension										
≤ 2 cord segments	38 (97,4%)*	7 (100%)	0 (0,0%)*	1 (11,1%)	5 (62,5%)	1 (33,3%)	0 (0,0%)	*	52 (76,5%)	**<0,001**
≥ 3 cord segments	1 (2,6%)*	0 (0,0%)	1 (100%)*	8 (88,9%)	3 (37,5%)	2 (66,7%)	1 (100%)	*	16 (23,5%)	
Gadolinium enhancement	26 (68,4%)	6 (85,7%)	1 (100%)	4 (57,1%)	6 (75,0%)	0 (0,0%)	0 (0,0%)	-	43 (66,2%)	0,119
Cord swelling	14 (35,9%)	4 (57,1%)	1 (50,0%)	6 (66,7%)	3 (37,5%)	0 (0,0%)	0 (0,0%)	-	28 (41,2%)	0,249
Brain MRI										
Normal	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	7 (87,5%)	1 (33,3%)	0 (0,0%)	-	8 (11,4%)	**<0,001**

Suggestive of MS	34 (85,0%)	5 (71,4%)	0 (0,0%)	1 (11,1%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	-	40 (57,2%)	
Non suggestive of MS	6 (15,0%)	2 (28,6%)	2 (100%)	8 (88,9%)	1 (12,5%)	2 (66,7%)	1 (100%)	-	22 (31,4%)	
CSF analysis										
Pleocytosis	14 (35,0%)	3 (42,9%)	2 (100%)	4 (50,0%)	1 (14,3%)	2 (66,7%)	0 (0,0%)	0 (0,0%)	26 (37,7%)	0,338
OCB +	30 (75,0%)	5 (71,4%)	0 (0,0%)	3 (33,3%)	2 (25,0%)	0 (0,0%)	0 (0,0%)	-	40 (58,8%)	**0,006**
IgG index > 0,5	25 (86,2%)	3 (75,0%)	1 (50,0%)	3 (60,0%)	4 (57,1%)	-	-	-	36 (76,6%)	0,338
VEPs										
Normal	20 (76,9%)	3 (60,0%)	1 (100%)	1 (25,0%)	6 (85,7%)	-	1 (100%)	-	32 (72,7%)	0,254
Increased latencies	6 (23,1%)	2 (40,0%)	0 (0,0%)	3 (75,0%)	1 (14,3%)	-	0 (0,0%)	-	12 (27,3%)	
EDDS at discharge	1.81±1.254	1.29±0.756	2.50±0.070	4.94±2.404	2.94±2.731	2.67±2.517	0.00	1.00	2,30±1,95	**<0,001**
Full Recovery	7 (17,5%)	4 (57,1%)	1 (50,0%)	1 (14,3%)**	2 (25,0%)	2 (66,7%)	1 (100%)	1 (100%)	19 (26,8%)	0,055
Relapses	27 (67,5%)	2 (28,6%)	0 (0,0%)	4 (57,1%)**	1 (12,5%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	34 (49,3%)	**0,013**
Myelitis relapses	15 (55,6%)	2 (100%)	-	2 (50,0%)	1 (100%)	-	-	-	20 (58,8%)	0,062
MSSS	1,85 [0,21-9,35]	0,53 [0,17-2,44]	2,96 [0,67-5,24]	7,75 [0,25-9,92]	2,55 [0,53-7,93]	0,67 [0,53-5,87]	0,67	0,35	2,01 [0,17-9,92]	0,190

Description: We evaluated all continuous variables in order to assess their normal distribution or not, EDSS at discharge and time of follow-up were the ones who showed a normal distribution considering both criteria. Meanwhile age at admission and MSSS only obey to kurtosis assumption. All continuous variables that did not show a normal distribution were described using median and minimum-maximum range and were analyzed using non-parametric tests to compare median results. All continuous variables that did show a normal distribution were described using mean and standard deviation and were compared using ANOVA tests and Levene's test to assure equal variances. Categorical variables were compared using chi-square or Fisher's exact test.

Not all supplementary diagnostic exams were performed in all patients, so percentages were presented considering only patients that were tested.

Abbreviations: MS: Multiple Sclerosis; CIS: Clinically Isolated Syndrome; ADEM: Acute Disseminated encephalomyelitis; NMOSD: Neuromyelitis optica spectrum disorders; IATM: Idiopathic acute transverse myelitis; PI: Post-infectious; SLE: Systemic Lupus Erythematous; Gender F:M – female:male; EDSS – Expanded Disability Status Scale; MRI – Magnetic Resonance Imaging ; CSF – Cerebrospinal fluid; OCB + : positive oligoclonal bands in cerebrospinal fluid; IgG – Immunoglobulin G; VEP – Visual Evoked Potentials; MSSS – Multiple Sclerosis Severity Score.

– not performed/not applied * no lesion was detected/one patient did not show any lesion on SC MRI; **two patients were lost follow-up (one died during ward admission and the other was a foreign patient).