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Original article

Lower urinary tract dysfunction in patients with multiple sclerosis: A post-void residual analysis of 501 cases

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ABSTRACT

Introduction: Lower urinary tract symptoms (LUTS) are common in individuals with multiple sclerosis (MS), and can have a significant impact on quality of life (QoL). Prevalence of LUTS in MS ranges from 32% to 96.8%, including storage or voiding symptoms or a combination of these. Post-void residual (PVR) is a very well-tolerated, non-invasive test for evaluating voiding dysfunction.

The aim of the current study was to describe the distribution of PVR volumes across MS subjects with and without LUTS and to examine relationships between storage symptoms, voiding symptoms, and PVR.

Methods: A large group of subjects (N = 501) completed a questionnaire on LUTS (current bladder management, number of urinary tract infections in the last year and urological investigations). A bladder ultrasound for PVR was performed and data were collected. We used Chi-Square and the Mann-Whitney non-parametric tests respectively for categorical and continuous variables in order to assess differences between symptomatic and asymptomatic groups. The differences of PVR by LUTS status were explored using the Mann-Whitney non-parametric test for independent samples.

Results: Overall mean PVR was 132.4 mL (PVR > 100 ml was considered an abnormal residual urine volume). Based on the LUTS questionnaire, 43 subjects (8.6%) were asymptomatic, while 458 subjects (91.4%) reported at least one LUTS. Storage-related symptoms were reported by 87.2% of subjects (437) and 65.1% (326) reported at least one voiding-related symptom. Two-third of subjects (66.5%) reported three or more LUTS. There was a statistically significant association between the presence of LUTS and the number of infections reported (p = 0.0015). The symptomatic group had significantly higher PVR than the asymptomatic group (p = 0.011). PVR significantly correlated with male gender, disability level and a progressive disease course.

Conclusion: Results showed a high prevalence of LUTS in subjects with MS and that storage symptoms are predominant. There was an association between the presence of LUTS and a progressive disease course. The relationship between LUTS, higher PVR and the severity of disease course indicates that a comprehensive clinical evaluation should include an assessment of both neurological and micturition disorders and, importantly, PVR should be measured at every clinical assessment, despite the presence or absence of LUTS.

1. Introduction

Multiple sclerosis (MS) is a progressive, demyelinating disease of the central nervous system, characterized by a wide range of symptoms. The frequency of urinary disorders in MS is widely recognized and prevalence ranges from 32% to 96.8%, appearing on average 6 years after the onset of the disease (Amarenco et al., 1995; Andrews and Husmann, 1997; Giannantoni et al., 1999; Koldewijn et al., 1995). About 10% of people with MS refer that a urinary problem is one of the first MS symptoms experienced (Phadke, 1990). Several studies also suggest that upper urinary tract involvement and kidney disease are not exceptional among people with MS (de Sèze et al., 2007). Neurologic control of the bladder is complex and requires coordination of the autonomic and somatic nervous systems (Betts et al., 1993). Functioning

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of the urinary tract to store and void urine are dependent on neural circuits in the brain, spinal cord and peripheral ganglia. Urinary tract control is peculiar with regard to its pattern of activity and the complexity of its neural regulation (De Groat, 2006). Adult neurogenic lower urinary tract dysfunction (ANLUTD) can cause some of the most common and disabling lower urinary tract symptoms (LUTS) related to MS (e.g. urinary urgency, frequency, nocturia, incontinence, chronic urinary retention (CUR), hesitancy, incomplete emptying, intermittency, straining to void, dysuria, diminished stream intensity) and often require specific interventions and at times, hospitalization, representing a relevant psychosocial burden (de Sèze et al., 2007). Micturition is a much more complex function than bladder contraction, requiring coordinated relaxation of the muscles of the pelvic floor based on the integration of autonomic and somatic efferent mechanisms (Morrison, 2005). This coordination is the result of learned behavior that develops during maturation of the nervous system. Neurologic control of the bladder is affected by MS lesions present at various levels of the central nervous system. Typical clinical urinary tract manifestations related to MS are influenced by the level of the lesion in the spinal cord. Lesions of the relevant suprapontine or spinal pathways regulating lower urinary tract functions affect the storage phase, resulting in reduced bladder capacity and detrusor overactivity. Lesions in the suprasacral spinal pathways may also lead to voiding difficulties and incomplete bladder emptying and also dangerously high pressure in the bladder (Panicker et al., 2015). A lesion in the sacral cord or infrasacral pathways results in voiding dysfunction associated with poorly sustained or absent detrusor contractions and/or non-relaxing sphincter (Panicker et al., 2015). Overactive bladder (OAB) syndrome, characterized by urinary urgency, usually accompanied by increased daytime frequency and/or nocturia, with urinary incontinence (OAB wet) or without (OAB dry) in the absence of urinary tract infection or other detectable disease (D'Ancona et al., 2019), is reported with a prevalence of 37–99% (Abrams et al., 2003; Kasabian et al., 1995; Porru et al., 1997). Obstructive symptoms are also frequently reported, affecting between 34% and 79% of subjects and result in chronic urinary infections in 25% of cases (Bakke et al., 1996; Bemelmans et al., 1991; Kasabian et al., 1995). Storage and voiding symptoms often coexist, affecting up to 59% of individuals with MS (Giannantoni et al., 1998). These clinical manifestations impact quality of life and are often associated with depressive symptoms, loss of work productivity, poor sleep quality and, in general, deteriorated overall health (Fowler et al., 2009; Litwiller et al., 1999). Problems related to micturition impede many people with MS from fully participating with family, friends and the community (Multiple Sclerosis Society of Canada, 2015).

Post-void residual (PVR) is the volume of urine left in the bladder at the completion of voiding (D'Ancona et al., 2019). PVR measurement is a non-invasive test for evaluating voiding dysfunction that can be performed with a portable bladder ultrasound device. PVR volume helps in the evaluation of many disease processes, including but not limited to neurogenic bladder, cauda equine syndrome, urinary outlet obstruction, mechanical obstruction, medication-induced urinary retention, postoperative urinary retention, and urinary tract infections (UTI) (Ballstaedt and Woodbury, 2020). Neurologists have found PVR useful for subjects with neurologic disease in particular in MS (De Ridder et al., 1997; Litwiller et al., 1999). The use of PVR as a clinical tool is currently not supported by robust evidence. In addition, threshold values delineating what constitutes MS-related urinary retention are poorly defined. The UK consortium defines abnormal residual urine volume as a PVR > 100 ml, while French guidelines propose a value > 300 ml (Denys et al., 2014; Fowler et al., 2009).

The aim of the current study was to describe the distribution of PVR volumes across MS subjects with and without LUTS and to examine relationships between storage symptoms, voiding symptoms, and PVR.

Table 1
Demographic and clinical data of sample.

		n = 501
Gender, n (%)	**M**	156 (31.1%)
	F	345 (68.9%)
Age in years, mean (SD)		56.0 (12.3)
Median (IQR)		56.0 (46–65)
Disease course	**RR**	77 (15.4%)
	SP	317 (63.3%)
	PP	107 (21.3%)
Disease duration, mean (SD)		21.4 (10.8)
Median (IQR)		20 (13–28)
EDSS score, mean (SD)		6.4 (1.6)
Median (IQR)		6.5 (6–7.5)
LUTS, n (%)		458 (91.4%)
PVR in mL, mean (SD)		132.4 (130.7)
Median (IQR)		102 (36–200)
Urological medication use, n%		65 (13.0%)
Urinary aids, n(%)		225 (44.9%)
UTI		133 (26.6%)

N, number; SD, standard deviation; EDSS, Expanded disability status scale; LUTS, Lower Urinary Tract Symptoms; PVR, Post-void Residual Volume; UTIs, Urinary tract infections; RR, relapsing-remitting; SP, secondary progressive; PP, primary progressive.

2. Materials and methods

Subjects were patients followed at the Italian MS Society (AISM) Rehabilitation Service in Genoa, Italy, who had undergone a clinical evaluation between January and July 2017. Exclusion criteria were pregnancy and indwelling or suprapubic catheterization. The study sample included 501 subjects with clinically definite MS. Demographic and disease-related information were collected, including age, gender, clinical course, disease duration, time of urinary symptom onset and the level of disability measured by the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) (Table 1).

Subjects' written informed consent was obtained and the study was conducted in accordance with the Declaration of Helsinki.

An ad hoc questionnaire composed by clinician assessed outcomes and patient reported outcomes was developed based on the International Continence Society definition of LUTS (D'Ancona et al., 2019; Gajewski and Drake, 2018). Questions focused on current urinary symptoms, bladder management (i.e. therapy, aids), number of documented infections in the previous year, urological investigations (i.e. urological evaluation, urodynamic test). The questionnaire is provided as supplementary material.

Ultrasound PVR measurement was performed by a physician using the following procedure: subjects were supine, with the head on a pillow and the lower abdomen exposed; an adequate amount of transmission gel was applied to the midline, superior to the symphysis pubis. Three separate ultrasound measurements were obtained and the highest value was included in the analysis. For the purpose of this study, PVR >100 ml was considered an abnormal residual urine volume (Fowler et al., 2009).

3. Statistical analyses

Demographic and clinical characteristics were analyzed as means, ranges and percentages. Differences between symptomatic and asymptomatic groups (detected by the questionnaire) were assessed using Chi-square and the Mann-Whitney non-parametric tests for categorical and continuous variables, respectively. The distribution of PVR by LUTS status was presented using box plots, while differences were explored using the Mann-Whitney non-parametric test for independent samples. PVR value was categorized using cut-offs of PVR ≥ 100 and ≥ 300 mL, as reported in the literature (Denys et al., 2014; Fowler et al., 2009). The chi-square test assessed differences between

groups. Spearman correlation coefficient determined the correlation between PVR and the number of LUTS. A multiple linear regression analysis was run to evaluate factors considered to influence PVR as a continuous variable. Due to a non-normal distribution, PVR values were converted using the square root (sqrt) function to run the regression model. In particular, simple linear regressions were used to analyze the relationship between PVR and socio-demographic and clinical characteristics. The independent variables that resulted as significant ($p < 0.20$) in the univariate analyses were included in a multivariate model using a stepwise backward model selection process with a pre-specified significance threshold of $p \leq 0.05$. Analyses were performed using Stata Version 15 (StataCorp, College Station, TX).

4. Results

Five hundred one subjects (68.9% female, $n = 345$) were included in the analysis. The mean age of the sample was 56.0 ± 12.3 years and mean MS duration was 21.4 ± 10.8 years. Seventy-seven participants (15.3%) had a relapsing-remitting disease course, 317 (63.3%) a secondary progressive course and 107 (21.3%) had primary progressive MS. The mean EDSS score was 6.4 ± 1.6 and mean PVR was 132.4 ± 130.7 mL. Fifty-one subjects (10.2%) were being treated with anticholinergic medication and 14 (2.8%) with an alpha blocker. The vast majority of subjects reported the presence of LUTS (91.4%, $n = 458$), while only 43 subjects out of 501 (8.6%) reported no LUTS (Table 1). Of subjects reporting LUTS, 130 (28.4%) had documented recurrent urinary tract infections (UTI), defined as finding of microbiological evidence of significant bacteriuria and pyuriaxii usually accompanied by symptoms such as increased bladder sensation, urgency, frequency, dysuria, urgency urinary incontinence, and/or pain in the lower urinary tract (Haylen et al., 2010). Storage-related symptoms were reported by 87.2% of subjects ($n = 437$) and 65.1% ($n = 326$) reported at least one voiding-related symptom. Two-third of subjects (66.5%, $n = 333$) reported three or more LUTS. The distribution of LUTS for the sample are reported in Fig. 1.

Among storage symptoms, the most frequently reported were urgency ($n = 304$, 60.7%) and urge incontinence ($n = 231$, 46.1%). Incomplete emptying ($n = 197$, 39.3%) and intermittency ($n = 164$, 32.7%) were the most frequently reported symptoms related to voiding. There was a significant association ($p = 0.0015$) between the presence of LUTS and the number of infections, with a higher number of infections in the symptomatic group compared to the asymptomatic group (0.9 and 0.07, respectively). There was a significant association between intermittent catheterization and UTI, in particular, 62% ($n = 31$) of subjects using catheterization had at least one UTI compared to 22.6% of subjects not using catheterization ($p < 0.001$). The presence of LUTS was more frequently associated with a primary progressive disease course ($p = 0.040$), a higher level of disability (mean EDSS of 6.4, $p = 0.011$) and UTI ($p = 0.002$) (Table 2).

Table 3 reports the distribution of urinary aids.

Table 2
Demographic and clinical characteristics by symptom status.

		Symptomatic Group ($n = 458$)	Asymptomatic Group ($n = 43$)	P value
Gender, n (%)	M	146 (31.9%)	10 (23.3%)	0.243
	F	312 (68.1%)	33 (76.7%)	
Age in years, mean (SD)		55.9 (12.4)	57.4 (11.7)	0.349
Median (IQR)		56 (46–65)	58 (50–66)	
Disease course	RR	66 (14.4%)	11 (25.6%)	0.040
	SP	289 (63.1%)	28 (65.1%)	
	PP	103 (22.5%)	4 (9.3%)	
Disease duration, mean (SD)		21.3 (10.9)	22.8 (10.1)	0.181
Median (IQR)		19 (13–28)	22 (17–29)	
EDSS score, mean (SD)		6.4 (1.5)	5.7 (1.9)	0.011
Median (IQR)		6.5 (6–7.5)	6.5 (5–6.5)	
UTI, n (%)	Yes	130 (28.4%)	3 (7.0%)	0.002
	No	328 (71.6%)	40 (93.0%)	

N, number; M, male; F, female; SD, Standard Deviation; P, probability; IQR, Interquartile Range; RR, Relapsing-Remitting; SP, Secondary Progressive; PP, Primary Progressive; EDSS, Expanded disability status scale; UTIs, Urinary tract infections.

4.1. Distribution of post-void residual volume (PVR) and correlations between self-reported LUTS symptoms and PVR

Boxplots show the distribution of PVR by presence and absence of LUTS. Both mean and median values of PVR observed in the symptomatic group were significantly higher than in asymptomatic group ($p = 0.011$) (Fig. 2).

There was a correlation between the number of LUTS symptoms and PVR (rho = 0.14, $p = 0.002$). Using the NHS and French MS retention definitions, 51.5% of subjects had a PVR ≥ 100 mL ($n = 258$), and 10.6% had a PVR ≥ 300 mL ($n = 53$). The proportion of subjects with

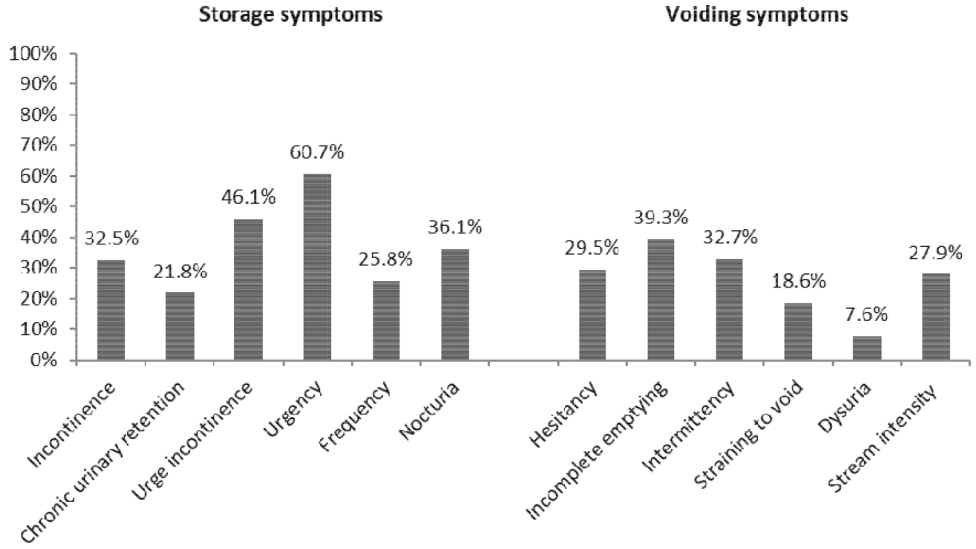

Fig. 1. Distribution of LUTS (storage and voiding symptoms).

Table 3
Frequency of the use of urinary management aids.

Urinary aid	N (%)
Intermittent catheterization (max 3/day)	50 (10.0%)
Urinary pot	14 (2.8%)
Diaper	166 (33.1%)
Urocondom	10 (2.0%)
*Other aids	7 (1.4%)

* Other aids (toilet seat, sanitary pad); N, number.

elevated PVR (≥100 mL) were different between groups ($p <= 0.001$), but there was no difference observed using a cut-off of PVR ≥300 mL ($p = 0.186$).

4.2. PVR, socio-demographic variables and clinical characteristics

Univariate analyses (Table 4) resulted in a significant association between PVR and gender (higher in males than females, $p < 0.001$), EDSS score (increased correlation with higher EDSS scores) and disease course (higher in progressive forms of MS compared to a relapsing-remitting course, $p = 0.005$ and $p = 0.041$ respectively). Moreover, PVR was higher in the presence of incontinence ($p = 0.007$), CUR ($p < 0.001$), feeling of incomplete emptying ($p = 0.015$) and diminished stream intensity ($p = 0.040$). The multivariate analysis showed that CUR ($\beta = 3.28$, $p < 0.001$), male gender ($\beta = 1.76$, $p = 0.001$) and higher EDSS score ($\beta = 0.93$, $p < 0.001$) were independently associated with higher PVR.

Table 4
Univariate linear regression of sqrt transformed PVR.

Univariate linear regression	β (95% CI)	P value
Gender (Female)	2.21 (1.07–3.35)	<0.001
Age	−0.01 (−0.05–0.03)	0.646
Disease duration	0.02 (−0.03–0.07)	0.512
EDSS score	0.99 (0.66–1.32)	<0.001
Disease course		
SP (RR)	2.18 (0.66–3.69)	0.005
PP (RR)	1.86 (0.08–3.64)	0.041
Urinary infection	0.63 (−0.58–1.84)	0.308
Urologic drugs use		
Antimuscarinic medication (no treat)	1.11 (−0.66–2.88)	0.219
Alpha blocker medication (no treat)	1.38 (−1.87–4.64)	0.403
Incontinence	1.57 (0.44–2.71)	0.007
Chronic urinary retention	3.59 (2.33–4.85)	<0.001
Urge incontinence	0.56 (−0.52–1.63)	0.310
Urgency	−0.14 (−1.12–0.96)	0.807
Frequency	0.68 (−0.55–1.90)	0.278
Nocturia	0.51 (−0.60–1.63)	0.365
Hesitancy	0.32 (−0.85–1.50)	0.591
Feeling of incomplete emptying	1.36 (0.27–2.45)	0.015
Intermittency	0.67 (−0.48–1.81)	0.252
Straining to void	1.24 (−0.13–2.61)	0.076
Dysuria	−1.20 (−3.22–0.82)	0.245
Stream intensity	1.25 (0.06–2.44)	0.040

PVR, Post-void residual volume was the dependent variable. Abbreviations: β- beta, P- level of significance, CI- confidence interval, EDSS- Expanded Disability Status Scale, SP- secondary progressive, RR- relapsing-remitting, PP- primary progressive. The reference category is reported in parentheses.

5. Discussion

The present study evaluated the distribution of PVR volumes in a large sample of subjects with MS, with or without self-reported storage and voiding-related LUTS. Results showed a high prevalence of LUTS, confirming what has been described in literature (Amarenco et al., 1995; Andrews and Husmann, 1997; Giannantoni et al., 1999; Koldewijn et al., 1995). Previous studies have shown that most individuals with MS will develop LUTS during the course of the disease (DasGupta and Fowler, 2002; Wiedemann et al., 2013). It is well known that LUTS are reported by subjects with MS even within a few years after diagnosis. However, in some subjects, these symptoms can be present from disease onset. Due to the progressive nature of MS, the prevalence of LUTS increases over time (de Sèze et al., 2007; Panicker et al., 2015). The present study delineated an association between the presence of LUTS and a progressive disease course. This

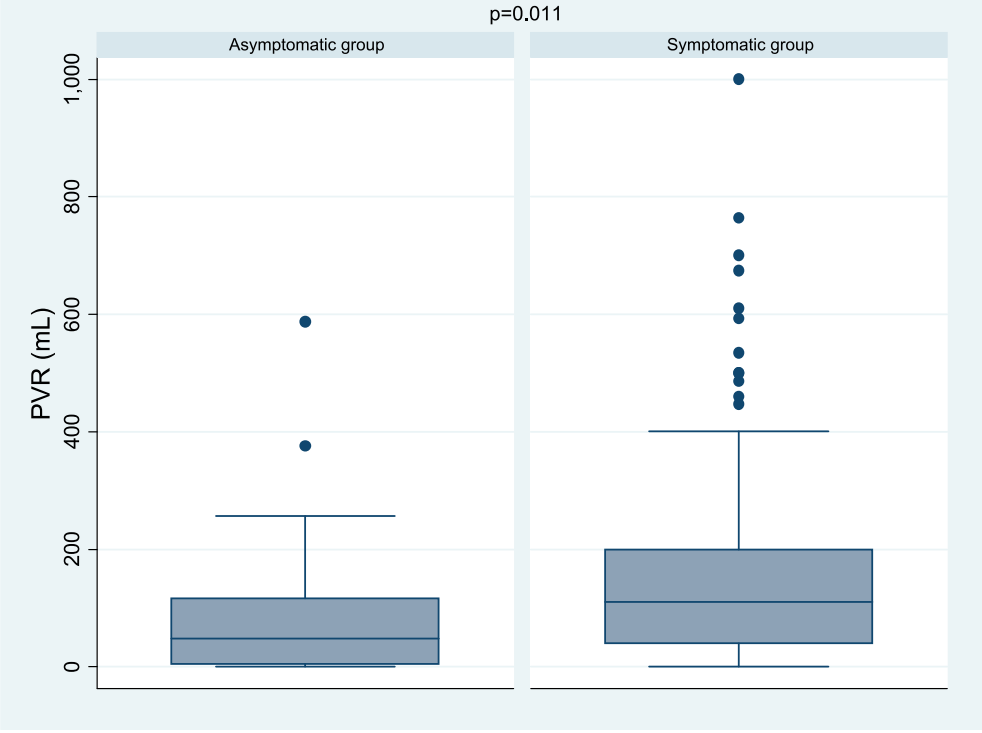

Fig. 2. Distribution of post-void residual volume (PVR) by presence and absence of LUTS.

may be explained, in part, by the fact that bladder changes occur over time (i.e. bladder neck and wall sclerosis, urethral stenosis, etc.) as well. Therefore, individuals with a progressive form of MS, and a greater number of disease years, are more likely to develop ANLUTD.

Most subjects in the study experienced storage symptoms. These results are in line with previous studies, which have reported that storage deficits are the most common type of urinary symptoms in MS (Del Popolo et al., 2008; Engeler et al., 2015; Tadayyon et al., 2012). Among the most reported symptoms, urgency and urge incontinence are the most prevalent problems related to an overactive bladder, while the feeling of incomplete emptying and intermittence are related to underactive bladder functioning. Greater than half of the sample reported three or more LUTS, although the number of self-reported urinary symptoms did not directly correlate with an increase in PVR volume.

Higher EDSS scores correlated with self-reported LUTS, highlighting an association between the presence of LUTS and more severe disability. A higher EDSS score is associated with an unfavorable urologic course, that subsequently increases the risk for higher urinary tract damage. This is particularly evident in primary progressive forms of MS that result in a very high level of disability.

Contrary to previous reports, PVR values were significantly higher in the symptomatic group than in the asymptomatic group (Dray et al., 2018). The incongruity may be due to different questionnaires used to screen for LUTS.

This study has some limitations. The lack of a micturition diary does not allow an adequate assessment of the person by integrating the PVR with the information obtained from the diary. This would allow a better and more complete management of ANLUTD. Also, it would be important to have objectively measured urodynamic data to early detect ANLUTD, to prevent structural changes typical of more advanced stages.

6. Conclusions

The present study demonstrated a strong correlation between an increase in PVR values and male gender, level of EDSS and disease course. These results confirm that the severity and duration of MS are risk factors of LUTS. Symptoms associated with higher PVR values were incontinence, CUR, incomplete emptying and reduced urinary flow intensity. In this regard, it seems prudent to assess for increased PVR in males with moderate-high EDSS, who report CUR, a feeling of incomplete emptying and/or urinary incontinence.

Further studies are needed to compare PVR data with a micturition diary and a urodynamic examination for a better NLUTD classification.

CRediT authorship contribution statement

Margherita Monti Bragadin: Writing - review & editing. **Roberta Motta:** Conceptualization, Investigation. **Michele Messmer Uccelli:** Writing - review & editing. **Andrea Tacchino:** Writing - review & editing. **Michela Ponzio:** Formal analysis. **Jessica Podda:** Writing - review & editing. **Giovanna Konrad:** Conceptualization. **Sara Rinaldi:** Conceptualization. **Marco Della Cava:** Writing - review & editing. **Mario Alberto Battaglia:** Supervision. **Giampaolo Brichetto:** Conceptualization, Investigation, Writing - review & editing.

Declaration of Competing Interest

All authors have nothing to disclose

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None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2020.102378.

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