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Investigation of tumefactive demyelination is associated with higher economic burden and more adverse events compared with conventional multiple sclerosis

Matthew Silsby[a], Pedro Sánchez[a,b], Judith M. Spies[b,c], Jane Frith[b], Joshua Barton[b], Heidi N. Beadnall[b,c], Michael H. Barnett[b,c], Stephen W. Reddel[a,b], Todd A. Hardy[a,b,*]

[a] Neurology Department, Concord Repatriation General Hospital, Sydney, New South Wales, Australia
[b] Brain and Mind Centre, University of Sydney, Sydney, New South Wales, Australia
[c] Department of Neurology, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia

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ABSTRACT

Background: Tumefactive demyelinating lesions occur as part of the spectrum of multiple sclerosis (MS), but can be difficult to distinguish from other large cerebral lesions such as neoplasm or abscess.
Objectives: To estimate the cost associated with diagnostic investigation of patients with tumefactive demyelination (TD), including associated morbidity, and compare this to more typical relapsing-remitting MS.
Methods: Retrospective review of medical records of patients seen between 2013 and 2018 in clinics at the Brain and Mind Centre, Sydney, Australia; a center with tertiary referral expertise in MS.
Results: Thirty-one patients with TD and 31 patients with MS were compared. The cost of investigating TD was more than 7.5 times higher per patient than MS ($18,300 vs $2418, $p < 0.01$). More patients in the TD group were admitted to hospital (22/31 versus 10/31) and ICU admissions only occurred in the TD group (10/22 versus 0/10). Brain biopsy was performed only in the TD group (7 patients), which contributed to cost differences and also accounted for differences in adverse outcomes.
Conclusion: The cost and morbidity related to investigating TD is higher than in typical MS. Improvements in the diagnosis of TD have the potential to improve health and economic outcomes.

1. Introduction

Relapsing-remitting multiple sclerosis (RRMS), is characterized by the dissemination of demyelinating lesions in time and space (Brownlee et al., 2017). Brain lesions identified on magnetic resonance imaging (MRI) are typically small (< 1 cm) and ovoid (Filippi et al., 2016).

Some patients with MS develop larger atypical demyelinating lesions as their first demyelinating event or later during their disease course. The term tumefactive demyelination (TD) is applied to demyelinating lesions larger than 2 cm in diameter (Hardy et al., 2016; Lucchinetti et al., 2008). TD lesions may present clinically with seizures, impaired consciousness, cognitive or cortical deficits, or focal neurological signs (Hardy, 2019).

TD lesions can pose a diagnostic challenge, especially in patients without a pre-existing diagnosis of MS. They are commonly mistaken for primary tumors or other space occupying lesions such as abscess, metastasis or infarction. Diagnostic uncertainty, and failure to consider tumefactive demyelination, can lead to extensive, unnecessary and risky investigations, including brain biopsy (Qi et al., 2015).

Here we evaluate the health economic impacts and morbidity of investigating TD and compare these with the costs for typical RRMS.

2. Materials and methods

2.1. Patients

Medical records from patients seen between 2013 and 2018 in clinics at the Brain and Mind Centre (BMC) in Sydney, Australia, a center with tertiary referral expertise in MS and other neuroimmunological conditions, were retrospectively reviewed with the search terms “tumefactive” and “pseudotumor”. All patients with the diagnosis of TD were included (“TD group”). TD was defined as any demyelinating lesion of ≥ 2 cm on MRI in any plane. TD lesions commonly occurred as a

* Corresponding author.
E-mail address: thardy@med.usyd.edu.au (T.A. Hardy).

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first, solitary demyelinating event, but patients with other demyelinating lesions and/or established MS who developed TD were also included. Each TD patient was paired with a patient diagnosed with conventional RRMS by the same neurologist within the same three months, according to 2010 McDonald criteria (Polman et al., 2011) ("MS group"). The rationale for this matching was to minimize bias attributed to differences in the investigation of MS or TD between neurologists.

2.2. Data collection

Ethical approval was obtained from the Human Research Ethics Committee Sydney Local Health District (LNR/17/RPAH/89). A waiver of consent was approved as data were collected retrospectively from routinely kept clinical records. All data were deidentified and securely stored in a password-protected database.

Demographic and clinical data collected included age at first presentation, time between symptom onset and diagnosis of TD or MS, any hospital stay, all outpatient specialist reviews, and major investigations until the day of confirmed diagnosis. All adverse effects arising from diagnostic processes were also collected. Data were incomplete for 3 patients in the TD group and 2 patients in the MS group.

In Australia, a universal health scheme (Medicare) covers the cost of access to health care in public hospitals and partially reimburses fees in the private system. In this study we estimated the cost of major investigations, procedures, nights in hospital, and specialist reviews using the Medicare Benefits Schedule Book (Australian Government, 2018) which provides a governmental value for each item. All costs presented are in Australian dollars (AUD, 1 AUD = 0.72 USD at the time of writing).

2.3. Statistical analysis

Comparisons between the two groups were performed using GraphPad Prism version 7.0b for Mac OS X, GraphPad Software, La Jolla California USA, www.graphpad.com. The groups were compared with the independent samples Mann-Whitney U test and reported as medians when data were non-normally distributed. The unpaired *t*-test was used for comparison of means when data were normally distributed, and the Chi-square of Pearson test, or Fisher exact test in the case of zero values, was used for frequencies. Statistical significance was set at $p \leq 0.05$ (2-sided).

3. Results

3.1. Patient demographics

Thirty-one patients with TD lesions and 31 patients with conventional MS were identified. There were no significant differences between the groups (Table 1). Age at first presentation was slightly older for the TD group (39 years old versus 34 years old, $p = 0.08$). The expanded disability status scale (EDSS) on presentation was similar (1.5 versus 1.0, $p = 0.70$).

Table 1
Patient demographics.

	TD Group	MS Group	*p* value
Number of patients	31	31	
Female gender – number (%)	19 (61)	25 (80)	0.09
Mean age at presentation – years	39	34	0.09
Median EDSS at presentation	1.5	1.0	0.70
Disease Modifying MS Therapy Commenced – number (%)	17 (55)	28 (90)	<0.01

3.2. Investigations

All patients in the TD and MS groups underwent MRI brain scans. In total there were 58 scans in the TD group and 51 in the MS group. MRI spine was performed in 20/31 TD patients and 25/31 MS patients ($p = 0.15$, Fig. 1).

The types of pathology tests ordered were similar between the two groups. An exception to this was myelin oligodendrocyte glycoprotein (MOG) IgG, which was ordered in 7/31 TD patients and only 1/31 MS patients ($p = 0.02$). None of the patients were positive for MOG or aquaporin-4 antibodies. Other invasive procedures including bone marrow biopsy (one patient) and gastrointestinal endoscopy (one patient) occurred only in the TD group.

Brain biopsy was performed in 7/31 TD patients compared with 0/31 MS patients ($p < 0.01$, Fig. 2). Features consistent with demyelination were reported in 6/7 of the biopsy cases; the remaining case was inconclusive and reported non-specific inflammation.

3.3. Admission and diagnosis

More patients in the TD group were admitted to hospital (22/31 vs 10/31, $p < 0.01$) of whom 10/22 in the TD group and 0/10 in the MS group were also admitted to the intensive care unit (ICU) ($p < 0.01$). Patients in the MS group were more likely to be admitted to hospital in the setting of higher initial EDSS scores on presentation. The mean hospital length of stay was longer in the TD group (4.4 versus 1.7 days, $p < 0.01$). The mean time to final diagnosis was 2.5 months in the TD group and 2.1 months in the MS group ($p = 0.54$) (Table 2).

3.4. Costs

Significantly more money was spent investigating patients in the TD group. The median expenditure in the TD group was $18,300 per patient, compared with $2418 per patient in the MS group ($p < 0.01$, Fig. 3). If only the cost of investigations (pathology, imaging, biopsy) was included, and hospital nights and outpatient specialist reviews were excluded, median expenditure was $2239 per patient in the TD group compared with $1632 per patient in the MS group ($p = 0.01$).

3.5. Morbidity

Adverse events occurred more often in the TD group including two patients with post-operative seizures after brain biopsy, and one patient who had an infected bone flap that required revision and prolonged antimicrobial therapy. Two TD patients required prolonged hospital admission including rehabilitation. There were two patients in the MS group who suffered low pressure headaches following lumbar puncture.

4. Discussion

The estimated direct cost of investigating a patient with a tumefactive demyelinating lesion is more than 7.5 times greater than the cost of investigating a patient with prototypic multiple sclerosis (TD group $18,300 per patient versus MS group $2418 per patient, $p < 0.01$). A major contributor to the disparity in cost relates to the number of nights spent in hospital while tests are performed. Furthermore, only patients in the TD group underwent brain biopsy, which also contributed to admissions to ICU.

The mean time to diagnosis was similar in the two groups despite patients in the TD group undergoing more investigations. A potential reason for the difference is that the MS patients were more often investigated in the outpatient setting.

Another important finding of our study is that investigational morbidity is higher in TD patients. Brain biopsy in the TD group, which did not occur in the MS group, led to adverse effects including seizures and post-operative infections.

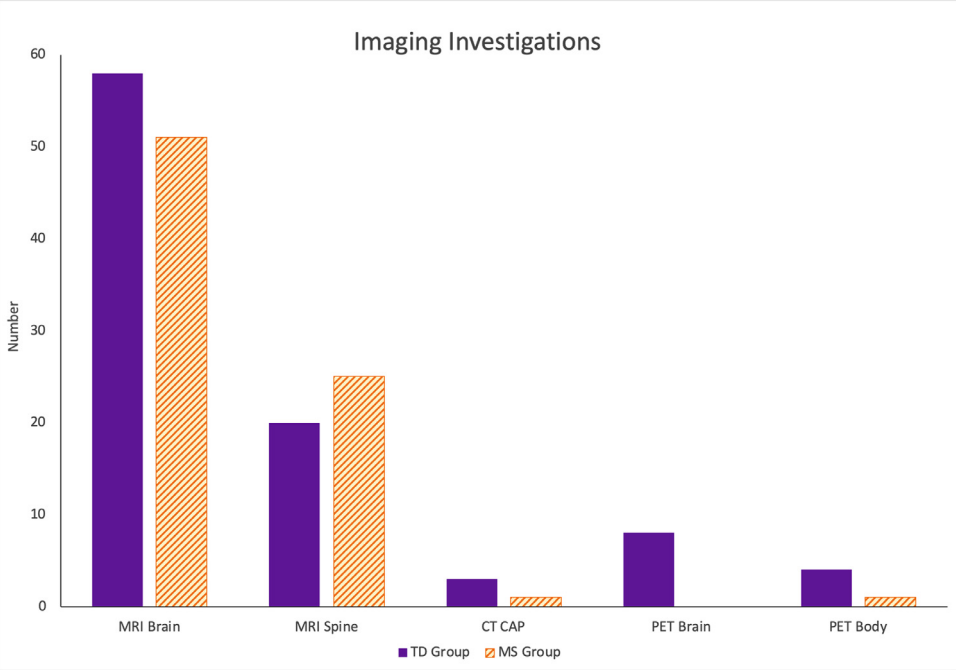

Fig. 1. Imaging investigations performed during the diagnostic process. There were no PET Brain scans ordered in MS patients.

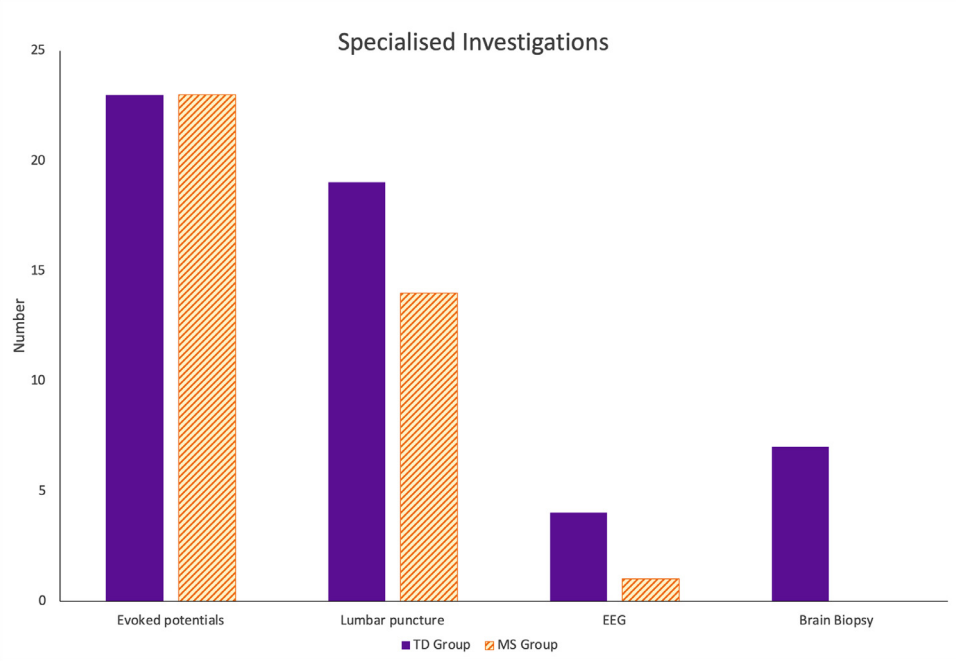

Fig. 2. Specialized investigations performed during the diagnostic process. There were no brain biopsies performed in MS patients.

Table 2
Admissions and time to diagnosis.

	TD Group	MS Group	*p* value
Admission to hospital (number of patients)	22	10	< 0.01
Admission to ICU (number of patients)	10	0	< 0.01
Mean length of stay (days)	4.4	1.7	< 0.01
Mean time to diagnosis (months)	2.5	2.1	0.54
Outpatient specialist reviews (mean number per patient)	2.7	2.3	0.13

According to recent estimates, TD lesions occur with a prevalence of 1.4% to 8.2% in patients with MS (Patriarca et al., 2016; Sánchez et al., 2017). In Australia in 2017, there were 25,607 patients living with MS (Ahmad et al., 2018). If we extrapolate our single center experience across Australia, the approximate cost of investigating TD lesions falls in the range of $6,560,513 to $38,425,864. This is substantial for healthcare systems where reductions in spending are a priority. Although we present data from a single center in Australia, we would surmise that the proportional difference in spending between investigating traditional MS and TD patients would be broadly applicable to other centers and health systems in the developed world.

This is the first study to examine the health economic implications

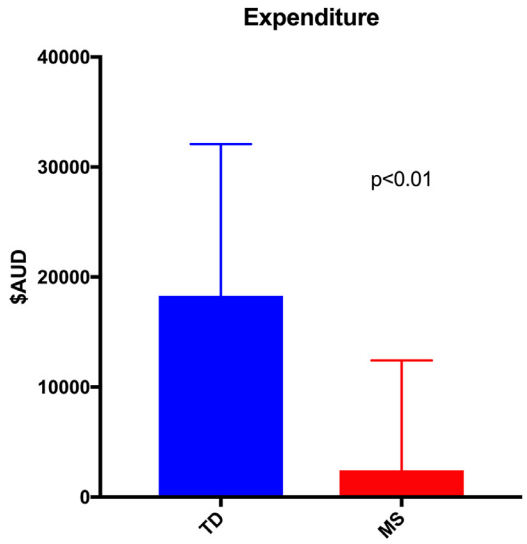

Fig. 3. Median per-person expenditure during investigation of tumefactive demyelination (TD) and typical multiple sclerosis (MS), measured in Australian dollars (AUD, 1 AUD = 0.72 USD).

of investigating TD lesions. Our results argue for the importance of further research to improve the diagnostic process so that brain biopsy can be avoided leading to improved economic and morbidity outcomes.

There are limitations of the present study. Costs were estimated based on the Medicare Benefits Schedule (Australian Government 2018), which may underestimate charges for privately insured patients. Limitations in our data meant expenditure per patient was also underestimated. We were unable to calculate the cost of medications as prescription data were incomplete. The cost of routine hospital pathology and x-rays were not included in the analysis. However, we believe these limitations would not change the proportional cost ratio between the TD and MS groups, and that we err towards underestimating the total cost. Lastly, an admission to hospital causes indirect costs due to loss of opportunity and dependency, not considered in this study.

5. Conclusions

Tumefactive demyelination poses a diagnostic challenge to the clinician. Our study demonstrates that the cost of investigating TD patients is more than 7.5 times that of investigating a 'conventional' MS patient. The more extensive investigations undergone by TD patients exposes them to iatrogenic morbidity, mostly related to brain biopsy. Further research directed at improving diagnosis of TD has the potential to favorably impact on the health and economic outcomes in this group of patients.

Conflict of interest

The authors declare that there are no conflicts of interest.

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