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Bone health in patients with multiple sclerosis relapses

Olwen Murphy [a,b,*], Michael S. Zandi [a,c], Nitzan Lindenberg [a], Elaine Murphy [d], Jeremy Chataway [a]

[a] Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, UCL Institute of Neurology, University College London and National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, London, United Kingdom
[b] Department of Neurology, Cork University Hospital, Wilton, Cork, Ireland
[c] Department of Neurology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge, United Kingdom
[d] Charles Dent Metabolic Unit, University College London and National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, London, United Kingdom

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ABSTRACT

Objectives: To evaluate the bone health and vitamin D levels of a cohort of patients with relapses of multiple sclerosis (MS) and to propose an algorithm for the management of bone health in this patient group.

Methods: We prospectively studied 56 consecutive patients from our acute relapse clinic. 3 patients were excluded from analysis as they were not deemed to have experienced an acute MS relapse. Bone health was assessed with vitamin D levels and Dual Energy X-ray Absorptiometry (DEXA) scanning (10 patients failed to attend for DEXA). Statistical analyses were used to compare groups and identify predictive variables. A review of the literature led to a proposed management protocol.

Results: Pre-relapse the baseline EDSS was ≤ 6.5 in all subjects, and < 4.0 in the majority (66%). Most received corticosteroids. 51% had low bone mineral density (BMD) as defined by a T-score less than -1.0 on DEXA scanning. Three were osteoporotic (T-score less than -2.5). Thirty one of fifty (62%) subjects were Vitamin D deficient (25(OH)D less than 50 nmol/L). A range of variables, including previous corticosteroid usage, were not significantly predictive of reduced BMD.

Conclusions: There was a high frequency of both low BMD and Vitamin D deficiency in this cohort of relatively young and largely ambulatory patients experiencing MS relapses. Current tools, such as the WHO FRAX algorithm, are inadequate in assessing bone status and fracture risk in this patient group, predominantly as they are focused on older age groups. We propose a simple clinical management algorithm.

1. Introduction

Metabolic bone disease is under-recognised and under-treated in multiple sclerosis (MS). There is a lack of evidence and guidance for the recognition and treatment of metabolic bone disease, particularly in patients with relapsing-remitting MS (RRMS) who may frequently be exposed to high doses of corticosteroids. Patients with MS (PwMS) have higher rates of fractures than the general population (Bazelier et al., 2011; Dennison et al., 2012) and reduced bone mineral density (BMD) compared to healthy controls (Sioka et al., 2011). Increasing neurologic impairment as categorised by the Kurtzke Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) is a key factor contributing to osteopenia and osteoporosis in PwMS (Zorzon et al., 2005; Weinstock-Guttman et al., 2004; Tüzün et al., 2003). However, while poor bone health is common in many chronic neurological diseases, reduced BMD has been identified even in the early stages of MS when patients are fully ambulatory and EDSS is low (Moen et al., 2011). High-dose methylprednisolone (intravenous or oral, 3–5 g) up to 2–3 times/year is a common treatment for relapses of MS, and is effective in reducing relapse duration (Myhr and Mellgren, 2009). Whilst long-term steroid treatment is a clear risk factor for osteopenia (and osteoporosis) as recognised in the FRAX algorithm; the position is much less clear for pulses of steroid which last for under a week. Short-term corticosteroid therapy has been shown to affect the biochemical markers of bone turnover in PwMS (Dovio et al., 2004), but the evidence for corticosteroid-induced osteopenia in this group is conflicting (Zorzon et al., 2005; Haugeberg et al., 2004; Hearn and Silber 2010).

Management of bone health in this population is challenging, as it is difficult to stratify fracture risk. The WHO FRAX calculator (www.shef.ac.uk/FRAX/) is a tool for predicting risk of fracture,

* Correspondence to: Cork University Hospital, Wilton, Ireland.
E-mail address: murphy.olwen@gmail.com (O. Murphy).

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however it has a number of limitations in the setting of MS. It is validated for a general population cohort over the age of 40 (Kanis et al., 2008), while in a typical relapse clinic the average age is 40 and women are pre-menopausal (Chataway et al., 2006). Steroids are only included as a risk factor in the FRAX calculation if the dose is at least 5 mg/day for more than 3 months, MS is not included as an independent risk factor, and it does not take into account Vitamin D deficiency which is associated with MS (Simon et al., 2012) and an important modifier of bone health. An alternative, the recent Qfracture tool, includes a wider age range and additional risk factors than the FRAX, (Hippisley-Cox and Coupland, 2012) however even with this tool the projection of the risk of fracture in this specific population is limited and likely to be an underestimation (Dobson et al., 2012). Bazelier et al. recently described a clinical risk score for the estimation of fracture risk for PwMS which is likely to give a better estimation of fracture risk in this specific population (Bazelier et al., 2012). However this scoring system needs further validation before routine use in a clinical context.

To examine these issues, we wanted to determine the bone status of a sequential cohort of patients attending an acute MS relapse clinic, who received high-dose steroid treatment. We aimed to identify any predictive variables for reduced BMD and create a simple management algorithm to improve quality of clinical care for this patient group.

2. Methods

The National Hospital of Neurology and Neurosurgery MS relapse service has been described before (McNicholas et al., 2012), but in brief, PwMS are tele-triaged by an MS-trained healthcare professional and then, if a significant relapse is occurring, proceed to a weekly ambulatory outpatient clinic. After assessment, if clinically indicated, a standard steroid regime of intravenous methylprednisolone 1 g/day for 3 days is used along with multi-disciplinary therapy input.

We included 56 consecutive patients from our clinic in this quality improvement study. Following medical assessment, 3 patients were deemed to have symptoms which were not compatible with an acute relapse and were excluded from statistical analysis. Demographic information was recorded for all patients, as well as details of MS type and duration, current medications including calcium/vitamin D supplementation, treatment with corticosteroids in the preceding two years (intravenous or oral form) and both pre-relapse and in-relapse EDSS. Lifestyle variables relevant to bone health were also recorded, including body mass index (BMI), smoking status, alcohol consumption, menopausal status and history of fragility fractures.

Blood tests (total 25-hydroxyvitamin D [25(OH)D] thyroid function tests, parathyroid hormone, renal, liver and bone profiles) were taken at the time of clinic attendance (between January and April). 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 were measured using liquid chromatography tandem mass spectrometry (LC-MS/MS), and these were combined to give total 25(OH)D. 25(OH)D levels below 7 nmol/L were arbitrarily scored as 5 nmol/L. Dual energy X-ray absorptiometry (DEXA) scanning was arranged within three months of attendance at clinic; DEXA T-scores and Z-scores were obtained for the hip, neck of femur and lumbar spine. T-scores compare BMD of an individual with that of a young healthy population, with osteoporosis defined as $SD \leq -2.5$ from the mean, and osteopenia as $SD \leq -1.0$ from the mean. A Z-score compares an individual's BMD to that of an age and sex matched population. 10 subjects failed to attend for scheduled DEXA scans, and comparing this group to the 43 subjects who did attend for DEXA, there were no significant differences in terms of gender, age, MS duration or EDSS.

FRAX scores were calculated using the online WHO FRAX Calculator (WHO, 2014). For patients under 40 the model calculates the probability of a fracture at age 40 (likely to result in an overestimation of fracture risk in younger subjects).

Comparisons between the groups were made with Student's *t* test for continuous variables and Fisher's exact test for categorical variables. Logistic regression was used to identify any predictive variables for osteopenia/osteoporosis, and linear regression to identify the lowest measured T score in an individual. BMI, age, sex, vitamin D levels, EDSS pre- and in-relapse, FRAX scores without bone density, smoking status and previous steroid exposure were entered as variables. Patients consented to inclusion and ethical approval was not required for this study as it was a service evaluation (NHS Health Research Authority, 2014).

3. Results

The cohort characteristics are described in Table 1. The mean age of all subjects was 39.6 years and the majority of patients (66%, 95% C.I. 52 to 80%) were fully ambulatory pre-relapse with an EDSS

Table 1
Demographic Characteristics of the Population.

		Female	Male	All subjects
Number		44	9	53
Age	Mean (years, s.d.)	39.7 (10.9)	41.3 (13.6)	39.4 (11.3)
	Range (years)	19–68	23–59	19–68
	Post-menopausal	3	–	3
BMI (*n*=48)*	Mean (kg/m^2, s.d.)	24.3 (5.3)	23.8 (3.5)	24.2 (5.0)
MS	Relapsing Remitting MS	40	6	46
	Secondary Progressive MS	1	3	4
	Unclassified	3	0	3
	Duration (years, s.d.)	8.7 (7.1)	14.2 (9.8)	9.9 (7.9)
	No. of relapses in previous 2 years	2.1	1.2	1.9
EDSS (*n*=44)*	EDSS pre-relapse < 4.0	73%	29%	66%
	EDSS in-relapse < 4.0	22%	14%	20%
Treatment (*n*=51)*	Calcium/vitamin D supplements	14%	22%	16%
	Bisphosphonate	2%	22%	6%
	Anti-convulsants	2%	22%	6%
	IFN/Glatiramer	48%	56%	49%
Methylprednisolone (*n*=47)*	Courses in previous 2 years (range)	2.6 (0–7)	2.3 (1–5)	2.5 (0–7)
Serum 25(OH)D (*n*=50)*	(nmol/L, s.d.)	48.2 (32.8)	33.3 (37.4)	45.5 (33.8)

* Subjects with missing data were excluded from analysis in these fields.