Reumatologia 2017; 55, 5: 251–255
DOI: https://doi.org/10.5114/reum.2017.71642

Relapse of polymyalgia rheumatica after a fall

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Abstract

Approximately half of PMR patients have a relapse with a necessity to increase GC dosages. The role of external factors in inducing PMR relapse have been poorly investigated.

We present a case-series of five PMR patients in remission with low doses of glucocorticosteroids (GC), who presented with relapse immediately after a fall. The assessment of PMR relapse was made using PMR-AS by Leeb and Bird, and a score > 9.35 was consistent with diagnosis of relapse. Gender, age, and cumulative dose of GC at the time of the fall were compared between the group of these five patients and a group of 41 PMR patients who had no PMR relapse after a fall: using the Fischer's exact test a significant difference was pointed out when the p-value was < 0.05. In our five PMR patients, the sharp worsening of clinical manifestations was always accompanied by a significant rise of the inflammatory indices and the increase of GC dosage (almost always 10 mg/day of prednisone) prompted a fast return (seven days as average) to the previous clinical and laboratory features. All other potentially responsible factors were excluded. Several months (6–10 months on average) after the fall, none of these five patients had a new relapse. No significant differences were found when we compared age, sex, and the cumulative dose of GC at the time of the fall between the group of patients with PMR relapse and the group of patients without.

The possibility of PMR relapse being realised immediately after a fall should be kept in mind in daily practice, especially when typical manifestations reappear immediately after a fall and other diagnostic hypotheses have been carefully excluded. The lack of important data (genetic factors, hormonal dosages, serum levels of IL-6 and/or serum soluble IL-6 receptor) in our case-series represented important limits for clarifying the nature of our observations and should be included in any subsequent study design on this argument. If our monocentric data are confirmed by multicentric data, the assessment of the risk of falls through specific scales should be an integral part of the visit of all PMR patients.

Key words: falls, polymyalgia rheumatica, relapse, disease activity score.

Introduction

Polymyalgia rheumatica (PMR) can be considered the most frequent inflammatory rheumatic disease in persons older than 70 years [1, 2]. Its diagnosis is based on recognition of a clinical syndrome consisting of pain and stiffness in the shoulder and pelvic girdle and morning stiffness lasting at least 45 minutes, as underlined in all diagnostic criteria proposed since 1979 [3, 4]. In most cases the erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) values are elevated, but the possibility that the clinical manifestations of PMR can be associated with normal values of ESR has been highlighted since 1983 by Ellis and Ralston [5]. Low-dose glucocorticosteroids (GC) are an effective treatment resulting in a striking improvement of symptoms and reduction of inflammatory indices but the rates and timing of response are not the same for all patients [6].

According to the recommendations for the management of polymyalgia rheumatica proposed in 2015 by the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) collaborative initiative [7], GC tapering should be according to a general scheme (Table I).

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Submitted: 24.08.2017; Accepted: 18.10.2017

Table I. GC tapering according to the schedule proposed by EULAR/ACR collaborative group [7]

Month	Daily dose of prednisone
1	12.5 mg (half of 25 mg tablet)
2	11.25 mg (two 5 mg tablets and two and a half 5 mg tablets on alternate days)
3	10 mg (two 5 mg tablets)
4	8.75 mg (two 5 mg tablets and one and a half 5 mg tablets on alternate days)
5	7.5 mg (one and a half 5 mg tablets)
6	6.25 mg (a quarter of a 25 mg tablets)
7	5 mg (one 5 mg tablet)
8	3.75 mg (one 5 mg tablet and half a 5 mg tablet on alternate days)
9	2.5 mg (half a 5 mg tablet)
10	1.25 mg (half a 5 mg tablet on alternate days)

Approximately half of PMR patients have a relapse with the necessity to increase GC dosages. The relapse occurs mostly between 6 and 12 months after diagnosis. Some of these have a repeated relapsing course with GC therapy for several years and sometimes for a lifetime [8]. The initial dosage of GC (< 15 mg/day of prednisone or prednisone equivalent) and its tapering speed (slow tapering = fewer relapses) can have an influence on relapse risk [9], but elevated levels of serum interleukin 6 (IL-6) during GC therapy has been considered the most significant risk factor [10, 11]. The role of external factors in inducing PMR relapse has been poorly investigated [8].

Case reports

We present a case-series of five PMR patients who visited our gerontorheumatological outpatient clinics in the last two years, who presented a relapse immediately after a fall. The assessment of PMR relapse was made using PMR-AS by Leeb and Bird, and a score > 9.35 was consistent with diagnosis of relapse. When ESR and CRP was found to be raised, the most important causes (with the exception of PMR) were carefully excluded using clinical, laboratory, and instrumental data. GC tapering was made using the schedule proposed by the EULAR/ACR collaborative group. The cumulative dose of GC at the time of the fall was compared between the group of these five patients and a group of 41 PMR patients who had no PMR relapse after a fall; using the Fischer's exact test a significant difference was pointed out when the *p*-value was < 0.05.

Case 1

A 77-year-old Caucasian woman affected by PMR in remission with 5 mg/day of prednisone fell while in her own home. The day after, she felt bilateral shoulder and neck pain associated with fever and morning stiffness lasting two hours. She had gone to the hospital emergency, where bone fractures were excluded. Routine laboratory tests pointed out the following: ESR = 81 mm/h; CRP = 55 vs. < 6 mg/dl, white blood cell count (WBC) = 8800/ml. She was advised to take a non-steroidal anti-inflammatory drug twice a day. We visited her two days later in our rheumatological outpatient clinic. The patient's PMR-AS score was 90 (VAS-p = 10; VAS-ph = 7; EUL grade 2). The patient was prompted to increase the prednisone dose to 10 mg/day for seven days and then return to 5 mg. After 10 days the PMR-AS score was 9.

Case 2

An 81-year-old Caucasian woman affected by PMR was in remission with 2.5 mg/day of prednisone. She fell and had a right ankle fracture. The next day she woke up unable to raise her arms, with violent neck pain and stiffness lasting about three hours. The patient's PMS-AS was 61 (CRP = 20 mg/dl: VAS-p = 10; VAS-ph = 10; EUL grade 3). A prednisone dose equal to 10 mg/day for five days, then reduced to 5 mg for other five days resulted in a PMR-AS score of 8.

Case 3

A 67-year-old Caucasian man affected by PMR, in remission induced by 5 mg/day of prednisone, fell from a staircase into his own garden. Accompanied to the hospital, a left wrist fracture of Colles was diagnosed. The day after, the patient was unable to get up from the bed due to violent girdle pain; he complained of morning stiffness lasting about 45 minutes. The patient's PMR-AS score was 33.5. After a week with 10 mg/day of prednisone, his PMR-AS score was 8.5.

Case 4

A 79-year-old Caucasian woman affected by PMR in remission induced by 5 mg/day of prednisone was invested by a cyclist. Accompanied in hospital, fractures were excluded and hospitalisation was recommended for observation. The day after, she was unable to get out of bed due to violent pains located at the back and shoulders. After a neurological examination and a TAC of the neck and skull, an injection of non-steroidal anti-inflammatory drug was made without any benefit. The rheumatologist diagnosed a PMS relapse and recommended that the prednisone dosage be increase to 12.5 mg/day. PMR-AS score was 103. After seven days the prednisone dose was reduced to 10 mg. The PMR-AS score was 9.

Case 5

An 82-year-old Caucasian woman in PMR remission with 2.5 mg of prednisone on alternate days, the night after having suffered a distorted trauma to the left knee, was unable to get out of bed to go to the bathroom and had to be helped by her daughter. The next morning, when we visited her, despite having taken an analgesic tablet in addition to 2.5 mg of prednisone, no improvement was recorded. The left knee was not swollen. The patient's PMR-AS score was 84. After five days of therapy with 10 mg/day of prednisone, PMR-AS was reduced to 9.

Discussion

Until today, the aetiology of PMR is unknown, although studies suggest that genetic factors including human leukocyte antigen shared epitope and polymorphisms in proinflammatory cytokines such as tumour necrosis factor-α and interleukin 6 cluster genes may be implicated [12]. In the early 2000s, some investigators highlighted that an altered adrenal responsiveness to the adrenocorticotrophic hormone (ACTH) stimulation was present in untreated PMR patients and they hypothesised that PMR could be considered as a disease of hypothalamic-pituitary-adrenal (HPA) axis. According to these authors, the alteration of this axis triggered activation of markers of inflammation such as IL-6, TNF-α, ESR, and CRP; GC administration correcting adrenal responsiveness to ACTH stimulation restored the normal inflammatory balance [13, 14]. A mechanism of immunity stimulation with small bleeding due to a fall could represent another hypothetical pathogenetic mechanism. In the first half of 20th century, so-called autohaemotherapy was recommended. It was based on intramuscular injections of the patient's blood samples. It is possible that a similar mechanism associated with small extravasation of blood contributed to enhanced inflammatory response in PMR patients, and relapse is secondary to this.

Recently a content analysis of data from the PMR Cohort Study in England explored patients' views on the causes of their PMR: from 363 responses to the questionnaire, 22 (6.06%) thought that a fall was the cause of their PMR [15].

As is well known, approximately half of PMR patients experience a relapse. Over the past 25 years, different criteria have been used to definite "PMR relapse": elevation of ESR and/or elevation of CRP (mm/dl), flare of PMR clinical features, response to GC; moreover, for each of these general criteria, differences in the variables and parameters were considered [16]. In 2004 an activity score for PMR (PMR-AS) was proposed by Leeb and Bird [17]. In this score, five variables must be calculated: CRP (mg/dl); Visual Analogic Scale (VAS) for the patient (from 0 – no disease activity to 10 – highest possible activity); VAS for the physician (0–10); morning stiffness time (MST) in minutes x 0.1; and ability to elevate the upper limbs (EUL) (3–0 where 3 = none, 2 = below shoulder girdle, 1 = up to shoulder girdle, 0 = above shoulder girdle). A PMR-AS > 9.35 authorised diagnosis of relapse. According to the same authors, a PMR-AS score between 0 and 1.5 was consistent with definition of PMR remission (Table II).

Table II. Remission and relapse based on PMR-AS by Leeb and Bird [table made by 2]

PMR-AS = CRP (mg/dl) + patient's pain assessment (VAS 0–10)* + physician's global assessment (VAS 0–10)† + morning stiffness (min) × 0.1 + EUL (0–3)‡	
Remission	0–1.5
Relapse	> 9.35 or a ΔPMR-AS score > 6.6

**0 = no pain; 10 = unbearable pain*
†0 = no disease activity; 10 = highest possible activity
‡0 = above shoulder girdle; 1 = up to shoulder girdle; 2 = below shoulder girdle; 3 = none
CRP – C-reactive protein; EUL – ability to elevate the upper limbs; VAS – visual analogue scale

In 2011, a Delphi-based expert consensus confirmed the usefulness of this score even if more than 80% of experts also judged the assessment of response to GC (even if a specified dose limit was not agreed upon) and hip symptoms (both not considered in PMR-AS) [16] to be important. For example, hips are involved in 50–70% of patients with PMR, and their assessment may improve the classification of those 10–30% of patients who lack shoulder symptoms [18].

Beyond definition and assessment of a PMR relapse, the role of external factors has been poorly investigated. In our case-series, five PMR patients experienced a relapse of disease after a fall with a significant contusional and/or distorting trauma. All these five patients were in remission with low (or very low) GC doses (2.5–5 mg on average). No significant differences were found when we compared age, gender, and the cumulative dose of GC at the time of the fall between patients with PMR relapse and patients without PMR relapse after a fall (Table III). As is well-known, GC can favour the fall through various mechanisms [19, 20], but the fact that their cumulative dose was overlapping in the two groups points out that this was not the factor influencing the occurrence of PMR relapse.

Definitely in our experience the only difference was that five patients had a sudden flare of the disease immediately after the fall, while the other 41 remained in remission despite having fallen.

The sharp worsening of clinical manifestations was always accompanied by a significant rise of the inflam-

Table III. Polymyalgia rheumatica and falls

	Patients with PMR relapse	Patients without PMR relapse	*P*-value*
Total	5	41	
Gender (F : M)	4 : 1	33 : 8	NS
Age (min.–max., years)	67–82	65–84	NS
Cumulative GC dose (mg of prednisone, min–max)	1838.5–2026	1844–2010	NS

**Fisher exact test. P-value was considered significant when < 0.05*

matory indices, and the increase in GC dosage (almost always 10 mg/day of prednisone) prompted a fast return (seven days as average) to the previous clinical and laboratory features. All other potentially responsible factors were excluded. Several months (6–10 months on average) after falling, none of these five patients had a new relapse.

To the best of our knowledge, few data regarding the relationship between PMR and falls are present in the literature: as already highlighted, the fall as a responsible factor is scarcely evaluated by PMR patients, and we found no data regarding the relationship between falls and PMR relapse.

The reason why a fall can determine a PMR relapse is until today speculative. It is possible that in some patients (with particular genetic basis) the fall may induce stress in such a way as to cause inadequate GC dose to be taken up and to alter the efficiency of the adrenal responsiveness to ACTH stimulation. The increase in GC dose would restore the *status quo*. The genetic factors (related, for example, to HLA antigens) could justify the fact that the falls can determine a PMR relapse only in a few patients (not in all, despite – for example – similar GC cumulative doses). The lack of evaluation of these factors (HLA antigens and hormonal serum levels) in our patients represented an important limit in our article.

Conclusions

Our short communication serves as a practical warning. To the best of our knowledge, it is the first time that the possibility that a fall can determine a relapse in PMR patients has been documented. This possibility should be kept in mind in daily practice, especially when typical manifestations reappeared immediately after a fall and other diagnostic hypotheses have been carefully excluded. Furthermore, if our monocentric data are confirmed by multicentric data, the assessment of the risk of falls through specific scales [21, 22] should be an integral part of the visit of all PMR patients. The lack of important data (genetic factors, hormonal dosages, serum levels of IL-6 and/or serum soluble IL-6 receptor) in our case-series represented important limits for clarifying the nature of our observations and should be included in any subsequent study design on this argument.

The authors declare no conflict of interest.

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