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Psychosis due to systemic lupus erythematosus: characteristics and long-term outcome of this rare manifestation of the disease

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Objective. To determine the prevalence, characteristics and long-term outcome of psychosis due to SLE defined according to the ACR nomenclature for neuropsychiatric (NP) syndromes.
Methods. All the patients who strictly fulfilled the ACR definition for psychosis due to lupus were identified within the 485 patients of our lupus cohort and retrospectively evaluated.
Results. Psychosis due to lupus was diagnosed in 11 (2.3%) patients. Lupus psychosis presented as the initial presentation of SLE in 60% of the patients and within the first year of the disease in 80% of the cases. All the patients developed psychotic symptoms within the context of multi-systemic lupus activity, with 90% of them having cutaneous involvement. Psychosis activity in our patients was associated with biological markers of lupus activity in 90% of the cases. The aPLS were observed in 10% of the cases. Seventy percent of our patients showed complete resolution of psychotic symptoms after a mean follow-up of 155 months. Long-lasting remissions were seen in all those patients. Chronic mild psychotic symptoms were observed in 30% of our patients.
Conclusion. Psychosis due to lupus is an uncommon event that usually occurs early in the course of the disease and is associated with other clinical and biological features of SLE. Long-term outcome appears to be favourable after intensive immunosuppressive treatment. This report highlights the need for prospective multi-centre studies to improve our knowledge and to help establish guidelines for the treatment of this rare complication of lupus.

Key words: Systemic lupus erythematosus, Neuropsychiatric lupus, Psychosis, Prevalence, Outcome.

Introduction

The classification criteria for lupus acknowledge just two central nervous system (CNS) features, psychosis and seizures [1, 2]. In reality, however, SLE may cause a wide range of neurological and psychiatric symptoms including those due to central, peripheral and autonomic nervous system and different psychiatric syndromes. In spite of this heterogeneity, the term neuropsychiatric (NP) lupus is usually used to refer to all of these manifestations. As the immunopathogenic mechanisms and clinical presentation of these syndromes are diverse [3], it would seem reasonable to assess them separately.

In 1999, the ACR developed a standardized nomenclature system for the NP syndromes of SLE for the purposes of classification and reporting [4]. It distinguishes three subsets of syndromes: psychiatric disorders, cognitive deficits and acute confusional states; neurological syndromes of the CNS and neurological syndromes of the peripheral nervous system [4]. Anxiety, mood disorder and psychosis are included into the term 'psychiatric disorders' and defined. Although psychosis, in the absence of offending drugs or electrolyte imbalance, is one of the 1997 ACR revised criteria for the classification of SLE [1, 2], specific data on the psychotic involvement in lupus are limited. Moreover, the long-term outcome of the patients with lupus psychosis is not well established either.

Using the ACR standardized nomenclature for the NP syndromes of SLE [4], we investigated all the patients in a large lupus cohort who were diagnosed with psychosis due to the disease in order to: (i) determine the prevalence of this disorder; (ii) report its clinical and laboratory manifestations and (iii) report the long-term outcome of these patients.

Patients and methods

The University College London Hospital (UCLH) cohort consists of 485 patients diagnosed with lupus and prospectively followed between January 1978 and December 2007. The female:male ratio in our cohort is 10:1. The predominant ethnicities are Caucasian, Afro-Caribbean and Asian (63, 19 and 10%, respectively). The mean duration of the SLE in our cohort at the time of the study was 14.1 ± 10.0 yrs.

All the patients included in our study fulfilled at least four of the 1997 ACR revised criteria for the classification of SLE [1, 2]. They met the criteria for psychosis described in the 1999 ACR nomenclature and case definitions for NP lupus syndromes [4]. Patients with psychosis associated with corticosteroids, other drugs or other metabolic conditions were excluded. As our main objective was to study the long-term outcome of these patients, patients with follow-up after the diagnosis of psychosis <12 months at the time of the study were also excluded.

Detailed clinical information on every patient at every outpatient attendance and at every inpatient admission has always been collected on our cohort. For the past 20 yrs this has been done as part of a BILAG assessment [5]. Patients and/or their relatives are also encouraged to phone in between appointments and/or bring their appointments forward if necessary. Thus, we think it very unlikely that a major feature as psychosis would have been missed. All the patients with symptomatic psychosis were assessed by a psychiatrist.

Patient data were thus retrospectively collected from medical and psychiatric records at UCLH. As we put in storage the notes of our deceased patients, we were able to review virtually the whole history of every patient. Data on demographics, age at SLE diagnosis, clinical lupus manifestations, types, duration and outcome of psychiatric symptoms, laboratory test results and therapy received during the psychotic events were recorded. Clinical features of lupus were defined according to the 1997 ACR revised criteria for the classification of SLE [1, 2]. ANAs were determined by indirect IF and considered positive if the titre was >1/80. Anti-double-stranded DNA (a-dsDNA) antibodies were measured by standard ELISA and defined as positive if more than twice the upper limit of normal (50 IU/ml on three occasions) or if

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positive by a *Crithidia luciliae* test. The aCLs were determined by ELISA and results were considered positive if medium-to-high titres (>20 IgG phospholipid units or IgM phospholipid units) were present on two or more occasions at least 6 weeks apart. Lupus anticoagulant (LA) activity was detected by coagulation assays (dilute Russell's viper venom time) according to the guidelines of the International Society on Thrombosis and Hemostasis [6].

Results

Eleven (2.3%) of the 485 SLE patients in the UCLH cohort were diagnosed with lupus psychosis. One of them had a follow-up after the diagnosis of psychosis <12 months and was excluded. The clinical characteristics and the results of the main diagnostic tests of the remaining 10 patients are detailed in Table 1.

Lupus psychosis

Nine of the patients with lupus psychosis were women and one was male. Seven were Caucasian and three were Afro-Caribbean. Mean age at diagnosis of SLE was 28.8 yrs (range 18–39 yrs). Mean age at diagnosis of the psychosis was 29.7 yrs (range 18–40 yrs). The average delay of the presentation of psychosis from lupus diagnosis was 10 months (S.D. ± 11.4). Eight (80%) of the 10 patients developed the psychosis within the first year after being diagnosed with lupus. Psychotic symptoms as the initial presenting feature of SLE occurred in 6 (60%) of the patients.

Eight (80%) of the 10 patients with psychosis had delusions with paranoid ideation in five; eight patients (80%) suffered hallucinations (auditory, visual and olfactory in eight, three and one case, respectively) and seven patients (70%) had both types of psychotic manifestations.

Clinical/analytical features of SLE

All the patients with lupus psychosis had six or more lupus criteria (range 6–7; mean: 6.7). The most frequently affected organ in patients with lupus psychosis was the skin. Nine (90%) of the patients had cutaneous involvement, malar rash being the most common cutaneous feature (80%). Skin vasculitis was present in half of the patients. Seven (70%) of the 10 patients had arthritis. Six (60%) of the 10 patients had some type of serositis pleural involvement being the most common. Only one (10%) of the patients had renal involvement (diffuse proliferative nephritis). Seven (70%) of the patients had at least one haematological criterion for lupus, lymphopenia (60%) being the most common. Serologically, 90% of the patients had high titres of ANA (ranging from 1/320 to 1/2560) and seven (70%) of them had raised levels of a-dsDNA (120–3600 IU/ml). Only one of the four patients tested had antibodies to ribosomal P proteins (anti-P). Only one (10%) of the patients had a positive aPL test. Nine (90%) of the 10 psychotic patients had very significant elevations of acute-phase reactants at the time of psychotic flares. Six (60%) and four (40%) of the patients with lupus psychosis had low haemoglobin and C3 levels, respectively. Cerebrospinal fluid analysis was performed in two cases with normal results.

Other NP manifestations

None of the 10 patients had psychosis as the only NP disorder. The most commonly reported additional NP manifestation was depression. Nine (90%) of the patients with lupus psychosis had depressive symptoms whose severity usually was mild–moderate although all patients needed to be treated with anti-depressants. In all the cases, depression occurred during or after the periods of activity of the disease. Anxiety, headaches, some degree of cognitive dysfunction and/or seizures were also reported in

TABLE 1. Clinical characteristics and results of the main diagnostic tests in 10 patients with psychosis due to lupus

Sex/ethnicity	Non-NP SLE manifestations	Psychotic manifestations	Other NP manifestations	Laboratory	Investigations
F/C	Arthritis, malar rash, skin vasculitis, lymphopenia	Paranoid ideation, auditory hallucinations	Cognitive dysfunction, depression	ESR↑, CRP↑, Hb↓ C3↓, ANA, a-dsDNA normal CSF	Abnormal MRI and EEG
F/C	Arthritis, malar rash, photosensivity, pleuritis	Delusions, paranoid ideation, auditory hallucinations	Anxiety, depression	ESR↑, CRP↑, ANA,a-dsDNA	–
M/C	Arthritis, malar rash, photosensivity, pleuritis	Auditory hallucinations	Depression	ANA, a-dsDNA	Normal MRI
F/C	Arthritis, malar rash, skin vasculitis, pleuritis, pericarditis, lymphopenia	Delusions of grandeur, paranoid delusions, auditory hallucinations	Cognitive dysfunction, anxiety, depression	ESR↑, Hb↓ ANA, a-dsDNA	Abnormal brain perfusion and EEG
F/AC	Malar rash, photosensitivity, oral ulcers, skin vasculitis lymphopenia	Paranoid delusions, auditory, visual and olfactory hallucinations	Anxiety, depression	ESR↑, CRP↑, Hb↓ C3↓, ANA, a-P-ribosomal protein	Abnormal brain perfusion, MRI and EEG
F/C	Arthritis, malar rash, photosensivity, thrombopenia	Delusions	Depression	ESR↑, ANA a-dsDNA	Abnormal brain perfusion and EEG
F/C	Myositis, photosensitivity, skin vasculitis, pleuritis, lymphopenia	Delusions	Depression, hypomania	ESR↑, CRP↑, Hb↓ C3↓, ANA, a-dsDNA	Normal MRI
F/C	Arthritis, malar rash, skin vasculitis, pleuritis, lymphopenia, thrombopenia	Visual, auditory hallucinations	Headache, depression	ESR↑, CRP↑	Normal MRI
F/AC	Arthritis, pleuritis, renal	Delusions, auditory hallucinations	Seizures	ESR↑, CRP↑, Hb↓ ANA, a-dsDNA, aPL	Normal MRI Abnormal EEG
F/AC	Malar rash, discoid lupus, photosensivity, lymphopenia	Paranoid delusions, visual, auditory hallucinations	Seizures,confusion, depression	ESR↑, CRP↑, Hb↓ C3↓, ANA normal CSF	Normal MRI

F: female; M: male; C: Caucasian; AC: Afro-Caribbean; Hb: haemoglobin; CSF: cerebrospinal fluid; anti-P: antibodies to ribosomal P proteins.

seven (70%) of the psychotic patients. One patient had hypomania, as well as depression.

Investigations on psychosis

Electroencephalogram. All five patients with lupus psychosis who had an electroencephalogram (EEG) had abnormal results, even though only one of them had had epileptic seizures. The most frequent finding in these patients (80%) was a generalized increase in slow activity on the EEG. One of those five patients had epileptiform activity.

Imaging investigations. Brain MRI was performed in seven of the patients with that being abnormal in two of them. The only other NP manifestations that these patients with that presented were depression (2), anxiety (1) and cognitive dysfunction (1). The reported findings were a small area of increased intensity signal in right frontal white matter and mild cortical atrophy.

Measurement of cerebral blood flow. All the three patients for whom this investigation was requested had a marked diffuse reduction in the brain perfusion measured by isotopic techniques. Two of the three patients had normal MRI studies.

Treatment at the psychosis diagnosis

Corticosteroids. Six (60%) of the patients needed treatment with high doses of intravenous methylprednisolone (1 g/day × 3 days) at the time of diagnosis with lupus psychosis. In all the cases, psychosis was the main lupus indication for this treatment. Four (40%) patients were treated with oral prednisolone (0.5–1 mg/kg/day).

Immunosuppressives. Four (40%) of the patients were treated with monthly intravenous cyclophosphamide (750–1000 mg × 1–3 months). Eight (80%) patients received treatment with AZA, four of them as first immunosuppressive agent and the other four as maintenance therapy after cyclophosphamide infusions.

Other SLE treatments. Three patients (30%) were treated with plasma exchange.

Psychiatric medications. All the patients were treated with anti-psychotic agents, chlorpromazine and haloperidol being the most commonly used. Anti-depressants and anxiolytics were indicated in nine and four patients, respectively.

Outcome of lupus psychosis

Table 2 shows the therapeutic strategy employed in every patient and the immediate and long-term outcome of the psychosis. The mean follow-up time from the diagnosis of lupus was 14.0 yrs (S.D. 8.5, range 2.6–25.8). The mean follow-up from the diagnosis of psychosis was 12.2 yrs (S.D. 8.0, range 2.1–25.8 months). At the end of the first year after the diagnosis of lupus psychosis, six (60%) of the patients had complete resolution of the psychiatric symptoms. However, three of them had a second psychotic flare up to 14 yrs later. The final outcome of the psychiatric symptoms at the end of the follow-up period was diverse. Long-term remission of psychosis was the most frequent finding. Seven patients (70%) achieved this with a duration ranging from 50 to 240 months (mean 120 months). Psychiatric medication was stopped in all of these patients without relapse of psychotic symptoms. Three of them had no treatment at all and three others were on low dose of prednisolone and AZA only for other different lupus manifestations. One patient died from a bacterial endocarditis after more than 10 yrs of remission. Two (20%) patients had chronic mild psychotic symptoms, one of them dying from metastatic colonic adenocarcinoma more than 30 yrs after the diagnosis of psychosis. Finally, one (10%) patient presenting with psychosis at the time of lupus diagnosis had severe psychiatric and non-psychiatric activity that persisted for 44 months until she died from infection after a burns injury.

Discussion

The prevalence of NP manifestations in SLE has been classically described as ranging between 14% and 75% [7, 8]. This wide range might be attributed to the heterogeneity of the different syndromes and the lack of standard definitions for them. The ACR nomenclature and case definitions for the NP lupus syndromes were developed for purposes of classification, enhancing clinical research, particularly multi-centre studies, and

TABLE 2. Treatment and outcome in 10 patients with psychosis due to lupus

Age (yrs) SLE/psychosis	Induction therapy	Short-term (<1 yr) outcome of psychosis	Maintenance therapy	Long-term outcome	FU (months)
18/18	MP/CYC High dose PRDL	Admission for 2 months at psychosis diagnosis, then resolution	Low-dose PRDL/AZA	SLE: >7 yrs in remission Psychosis: >7 yrs in remission	96
26/26	Medium dose PRDL	Partial remission	Low-dose PRDL	SLE: low general and articular activity Psychosis: low chronic activity	250
36/37	Medium dose PRDL/AZA	Partial remission	Low-dose PRDL/AZA	SLE: low articular and skin activity Psychosis: low chronic activity	32
23/27	MP Plasmapheresis High-dose PRDL	Admission for 3 months at psychosis diagnosis, then resolution	Low-dose PRDL No treatment for >10 yrs	Second psychotic flare at 5 yrs SLE: >10 yrs in remission Psychosis: >15 yrs in remission	290
29/29	Medium dose PRDL/AZA	Partial remission	Low-dose PRDL/AZA	SLE: severe general and skin activity Psychosis: chronic activity with 4 flares in the 4 yrs after SLE diagnosis	44
39/40	High dose PRDL/AZA	Resolution	Low-dose PRDL No treatment for 4 yrs	2nd psychotic flare at 14 yrs	240
22/22	MP/AZA Plasmapheresis High dose PRDL	Resolution	Low-dose PRDL/AZA; no treatment for >8 yrs	SLE: >10 yrs in remission	144
35/35	MP/CYC Plasmapheresis	Partial remission	Low-dose PRDL/AZA	SLE: moderate general/joint activity Psychosis: low chronic activity for the first 5 yrs then >20 yrs in remission	310
35/35	MP/CYC High dose PRD	Resolution	Low-dose PRDL/AZA; no treatment for >10 yrs	2nd psychotic flare at 2 yrs SLE: >10 yrs in remission Psychosis: >10 yrs in remission	200
25/28	MP/CYC High dose PRDL	Resolution	Low-dose PRDL/AZA	SLE: low activity Psychosis: >4 yrs in remission	84

FU: follow-up since SLE diagnosis; MP: intravenous methyprednisolone (1 g/day, three consecutive days); CYC: cyclophosphamide; PRDL: prednisolone.

TABLE 3. Prevalence of psychosis due to lupus reported after the publication of the 1999 ACR nomenclature and case definitions for neuropsychiatric lupus syndromes

Reference	Patients *n*	Female/male	Ethnicity, %	NP, *n* (%)	Psychosis *n* (%)
Ainiala *et al.*, Finland [9]	46	5.5/1	ND	42 (91)	0 (0)
Mok *et al.*, China [10]	518	7.7/1	Chinese, 100%	96 (19)	56 (11)
Brey *et al.*, USA [11]	128	15/1	Hispanic/W/B/O 56%/30%/8%/3%	96 (75)	6 (4)
Jonsen *et al.*, Sweden [12]	117	5.8/1	Caucasian/Chinese 99%/1%	44 (38)	9 (7)[a]
Afeltra *et al.*, Italy [13]	61	6.6/1	ND	44 (72)	0 (0)
Sanna *et al.*, UK [14]	323	19/1	ND	185 (57)	25 (7)
Hanly *et al.*, Canada [15]	111	6.4/1	Caucasian/Asian/B/O 92%/4%/2%/2%	41 (37)	3 (2)
Mok *et al.*, China [17]	282	10/1	Chinese 100%	65 (23)	15 (5)
Appenzeller *et al.*, Brazil [18]	537	ND	ND	ND	59 (11)
UCLH, London, 2008	485	10/1	Caucasian/AC 70%/30%	ND	11 (2.3)

NP: neuropsychiatric; ND: no data; W: white; B: black; O: other; AC: Afro-Caribbean. [a]Includes psychosis or endogenous depression.

reporting [4]. Since its publication in 1999, it might have been expected that more homogeneous data on the prevalence of the different NP lupus syndromes would have emerged. However, it ranges widely from 19% to 91% in the different series reported after that date [9–17]. More specifically, the reported prevalence of lupus psychosis, the concern of our study, has also varied from 0% to 11% since that year (Table 3).

Psychosis is defined as a severe disturbance in the perception of reality characterized by delusions and/or hallucinations, in the absence of delirium, causing clinical distress or impairment in social, occupational or other relevant areas of functioning. This is not a common feature in SLE. There are very few studies specifically exploring the characteristics of this psychiatric complication of SLE published after the ACR standardized definitions were developed. There is also a paucity of data on the long-term outcome of lupus psychosis. Our study is a careful retrospective attempt to investigate the prevalence, timing, characteristics and the long-term outcome of psychosis occurring in a large cohort of lupus patients in a single centre.

According to the 1997 ACR revised criteria for SLE [1, 2] and the 1999 ACR case definitions for NP lupus syndromes [4], we report that 11 (2.3%) of our 485 lupus patient cohort experienced at least one psychotic episode related with their disease. Ainiala *et al*. [9] and Afeltra *et al*. [13] described 0% of the lupus patients of their series having psychosis but these results could be attributed to the small size of their samples: 46 and 61 patients, respectively. If we exclude these two series, the most commonly reported prevalence is about 2- to 5-fold higher than thatin our series [10–12, 14, 17, 18]. Possible causes of this difference include the different methods employed for the selection and assessment of the population and its diverse ethnic background. However, we think that the main reason could be related to the interpretation of the ACR NP lupus definitions. The ACR Committee adopted the terminology of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [19]. Therefore, the case definition for lupus psychosis is based on the DSM-IV entity 'psychosis due to a general medical condition' (DSM-IV 293.81/82) that excludes 'schizophrenia' to be considered as a primary disease and also the DSM-IV category 'brief psychotic disorder' to be considered a reaction to an extremely stressful event or trauma. Bipolar disorder is considered in the DSM-IV category 'mood disorder' and also excluded. In our lupus cohort, we identified one patient with schizophrenia, one patient with possible brief psychotic disorder and two patients with bipolar disorder who were not included in our study. However, establishing a precise psychiatric diagnosis may be difficult in daily practice. In fact, the members of the ACR Committee had the highest degree of disagreement in defining psychosis and other diffuse CNS disorders [4]. Overall, however, it is evident that psychosis is an uncommon feature in SLE patients.

In our patients, psychosis was usually an early finding in the course of the disease. As reported before the publication of the ACR NP lupus definitions, psychiatric symptoms can precede the onset of lupus or occur at any time during its course [20, 21]. However, there are very few data reported after 1999 assessing the timing of this complication of the disease. Recently, the diagnosis of lupus psychosis at the onset of the disease has been described in one-third of the cases of a large series of SLE patients [18]. As the mean length of follow-up in that series is short (~5 yrs), it is difficult to assess the frequency of new or recurrent episodes occuring late in the course of the disease. After a mean follow-up of 14 yrs, 60% of the patients of our cohort suffered psychosis at the moment of the onset of SLE and 80% within the first year of the diagnosis of the disease. Thus, psychosis due to lupus appears to be rarely a late complication of the disease.

We observed that psychosis in lupus usually occurs within the context of florid activity of the disease, associated mainly with cutaneous and haematological manifestations and analytical markers of lupus. However, only one of our patients had renal involvement. Nearly all our psychotic patients had some kind of cutaneous involvement mainly malar rash (90%) and clinical signs of skin vasculitis. The frequency of skin involvement in our patients with psychosis is higher than that in our whole lupus cohort in which the overall prevalence is of 68% (unpublished observations). From a serological perspective, 90% of our psychotic patients had high titres of ANA and/or anti-dsDNA antibodies. However, other autoantibodies associated with NP lupus manifestations nearly were found in our study. Only one of our psychotic patients was positive for aPL. It contrasts with approximately one-third of the patients in our whole cohort who are aPL positive (unpublished observations). Although the association of positivity of aPL with NP lupus has been reported [13, 14], there are no convincing data to suggest that they are useful in the diagnosis of lupus psychosis.

There is no standardized treatment for lupus psychosis. In our cohort, we have used a variety of therapies. All the patients received corticosteroids and anti-psychotics and 90% of them received an immunosuppressive agent. We used plasma exchange in three refractory cases. To the best of our knowledge, there are no controlled trials assessing any treatment strategy in the management of lupus psychosis. Several small studies have reported the benefit of the use of corticosteroids and different immunosuppressive strategies in patients with NP lupus [22–27]. More recently, one study reported the efficacy and tolerability of rituximab in the treatment of patients with lupus psychosis [28].

Little is known about the outcome of psychosis due to lupus. One year after the diagnosis and treatment, 60 and 40% of our patients with lupus psychosis showed complete resolution of their psychiatric symptoms or chronic psychotic activity, respectively. Interestingly, those achieving complete remission had the most severe psychotic manifestations at the onset, requiring the most aggressive therapeutic approach with intravenous methylprednisolone pulses in five cases. Three of these patients with good response to the treatment presented with a second acute psychotic flare up to 14 yrs after the diagnosis. In three of the four patients with chronic psychotic activity at the first year of the diagnosis, the psychiatric symptoms were occasional and mild in severity.

The other patient developed several psychotic flares until her death 4 yrs after the diagnosis.

In our study, we report that 70% of the patients achieved complete remissions of lupus psychosis for up to 20 yrs. More than one-half of these patients have been free of psychiatric symptoms and without any treatment for 4–10 yrs. Interestingly, we observed a specific pattern in the long-term evolution of the psychiatric involvement in our patients. We found that all the patients whose psychosis had a good response to the treatment at the time of diagnosis remained asymptomatic at the end of the follow-up period with long-lasting remissions. Overall, the long-term outcome of psychosis due to lupus appears to be favourable.

As our study is retrospective and the size of the sample is small, our findings must be interpreted with caution. However, in the paucity of clinical data on this rare outcome, we think that this investigation will be of interest to the clinicians in the field. From our carefully observed patients followed up for many years we conclude that psychosis due to lupus is a rare complication of the disease. It usually occurs in the early stage of SLE and within the context of florid clinical and serological activity of the disease. Long-term outcome of lupus psychosis appears to be favourable after intensive immunosuppressive treatment. We stress the need for prospective multi-centre studies to acquire better knowledge and develop guidelines to optimize the treatment of psychosis due to lupus.

Rheumatology key messages

- Psychosis due to lupus is a rare manifestation of the disease.
- If you look after these patients appropriately during the active phase, the long-term outcome is good with low chances of another flare.

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