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Characteristics of pediatric recurrent erythema multiforme

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Abstract

Background: Erythema multiforme (EM) is an acute condition characterized by distinctive target lesions of the skin often accompanied by mucosal ulcers. A subset of individuals experience frequent episodes of recurrent EM, which is rare and poorly understood, especially in children.

Objective: To characterize clinical features, laboratory findings, and treatment responses of pediatric recurrent EM.

Methods: A retrospective chart review was conducted at the Children's Hospital of Wisconsin in Milwaukee, Wisconsin (2000-2015) and the Mayo Clinic in Rochester, Minnesota (1990-2015). Inclusion criterion was a diagnosis before age 18 years with recurrent EM, defined as a symmetrically distributed, fixed eruption, including target lesions, with or without mucous membrane involvement, occurring on at least three occasions. A literature review was conducted to include individuals who met the inclusion criterion.

Results: Twenty-six patients were included, of whom 16 (62%) were male. The median age of onset was 9.1 years (range 0-15.7 years). Nine patients (35%) required hospitalization. Herpes simplex virus testing was positive in 9 of 17 (65%) patients. Remission was achieved in 5 of 16 (31%) patients while taking suppressive antivirals. Eight patients received continuous anti-inflammatory treatment, two (25%) of whom experienced remission.

Conclusion: This study of pediatric recurrent EM found a greater male predominance, more hospitalizations, fewer cases caused by herpes simplex virus, and a lower response to immunosuppression in children than in the general population.

KEYWORDS
children, chronic erythema multiforme, erythema multiforme, recurrent erythema multiforme

1 | INTRODUCTION

Erythema multiforme (EM) is an acute, immune-mediated condition characterized by distinctive target lesions of the skin and often accompanied by ulcers or bullae involving the oral, genital, or ocular mucosa. Although most patients experience only one outbreak in a lifetime, a subset of patients has repeated episodes of EM known as recurrent EM. Although previous studies of recurrent EM have been performed, recurrent EM in children is not well understood. The aim of this retrospective cohort study was to clarify the features of pediatric recurrent EM, including clinical characteristics, causes, and response to treatment.

2 | METHODS

2.1 | Data collection

Institutional review board approval was obtained at the Children's Hospital of Wisconsin, Milwaukee, Wisconsin, and the Mayo Clinic, Rochester, Minnesota. *International Classification of Diseases, Ninth Revision*, code 695.1 was used to identify children who were diagnosed with EM at the Children's Hospital of Wisconsin and Mayo Clinic. Inclusion dates of January 1, 2000, to March 27, 2015, were used at the Children's Hospital of Wisconsin and January 1, 1990, to June 1, 2015, at the Mayo Clinic. All charts were reviewed to identify children meeting the predetermined definition of recurrent EM, which was "symmetrically distributed, fixed eruption, including target lesions, with or without mucous membrane involvement, occurring on at least three occasions."[1] We examined medical records to extract patient characteristics, clinical characteristics, disease duration, laboratory tests and results, treatments, and response to treatments.

Treatments were defined as intermittent (given only during an outbreak) or continuous (given to prevent disease recurrence). We evaluated the response to treatment modalities. Complete response (CR) was defined as total resolution of lesions during intermittent treatment or no new lesions during continuous treatment. Partial response (PR) was defined as healing of some lesions during intermittent treatment or a decrease in the frequency and severity of lesions during continuous treatment. No response (NR) was defined as persistence of lesions during intermittent treatment or no change in the frequency and severity of lesions during continuous treatment.

2.2 | Literature review

A literature review of pediatric recurrent EM was conducted. The PubMed database was queried using the search term "recurrent erythema multiforme," and case studies were selected that included children with recurrent EM according to the definition.

TABLE 1 Patient and disease characteristics

Characteristic	Value
Patient, n (%)	
Sex	
Male	16 (62)
Female	10 (38)
Race and ethnicity	
White	16 (62)
Black	4 (15)
Hispanic	2 (8)
Unknown	4 (15)
Disease	
Age at disease onset, years, median (range)	9.1 (0-15.7)
Episodes per year, median (range)	2 (1-11)
Patients requiring hospitalization, n (%)	9 (35)
Number of hospitalizations, median (range)	1 (1-4)
Duration of follow-up, years, median (range)	2.3 (0-24.9)
Cutaneous involvement, n (%)	24 (92)
Upper extremities	22 (85)
Lower extremities	19 (73)
Face	16 (62)
Trunk	12 (46)
Mucus membrane involvement, n (%)	20 (77)
Oral involvement	20 (77)
Lips	18 (69)
Buccal mucosa	12 (46)
Tongue	11 (42)
Soft palate	8 (31)
Gingiva	8 (31)
Genital involvement	6 (23)
Male	5 (83)
Female	1 (17)
Ocular involvement	1 (4)

3 | RESULTS

3.1 | Clinical characteristics

Twenty-six patients met the study inclusion criteria, of whom 16 (62%) were male. The median age of onset was 9.1 years (range 0-15.7 years). The median number of episodes per year was 2 (range 1-11). The median duration of follow-up was 2.3 years (range 0-24.9 years). Nine patients (35%) were hospitalized for their EM, including all six initially diagnosed with Stevens–Johnson syndrome (SJS).

Nearly all patients (92%) had cutaneous involvement, most commonly on the upper extremities (85%), lower extremities (73%), and face (62%). Oral involvement occurred in 20 (77%) patients, most frequently on the lips (69%). Genital involvement occurred in six (23%) patients, of whom five were male and one was female. Ocular involvement occurred in one (4%) patient. Clinical and disease characteristics are displayed in Table 1.

3.2 | Laboratory tests

In all, 17 (54%) patients had one or more tests for herpes simplex virus (HSV) during a flare. Of the 11 patients who had serum antibody testing, 6 (55%) tested positive for anti-HSV immunoglobulin G (IgG) alone and 3 (27%) for anti-HSV IgM and IgG. Skin biopsies were performed in 10 patients and the results were consistent with EM in 9 (90%). The specimen not consistent with EM showed lichenoid dermatitis, but the patient's clinical features were supportive of EM. Laboratory tests and results are displayed in Table 2.

3.3 | Treatment

Seventeen (65%) patients received at least one course of systemic corticosteroids during an active episode of recurrent EM.

TABLE 2 Laboratory test results

Laboratory test	Total, n (%)	Positive
Herpes simplex virus		
PCR		
Oral	9 (35)	0 (0)
Skin	9 (35)	1 (11)
Serum	2 (8)	2 (100)
Serum IgM	11 (42)	3 (42)
Serum IgG	11 (27)	6 (55)
>1 HSV test	17 (54)	9 (65)
Mycoplasma PCR	3 (12)	0 (0)
Human immunodeficiency virus enzyme-linked immunosorbent assay	3 (12)	0 (0)
Epstein–Barr virus monospot	2 (8)	1 (50)

PCR, polymerase chain reaction; Ig, immunogobulin.

Immunosuppressants and anti-inflammatory agents were used in eight (31%) patients with severe and frequent recurrent EM. Two (25%) patients had a CR, one each to dapsone and azathioprine. Treatments and responses are displayed in Table 3.

3.4 | Literature review

Thirty-one cases of pediatric recurrent EM have been reported in the literature, although the nine children in Weston and colleagues' study[15] and the five in Siedner-Weintraub and colleagues' study[16] did not have sufficient data regarding patient characteristics, lesion distribution, and response to treatment for inclusion.[2-14] The remaining 17 cases are summarized in Table 4.

The 26 cases of pediatric recurrent EM from the current study and the 17 previously reported cases are analyzed in aggregate in Table 5. Most reported patients have been male (n = 30 [70%]), with a median age of onset of 9.1 years (range 0-18 years) and a median of 1.8 episodes per year (range 1-11).

In all, 25 (58%) patients had one or more tests for HSV (HSV polymerase chain reaction [PCR], HSV-1 direct fluorescent antibody, or anti-HSV IgM/IgG) during a flare, with 16 (64%) having at least one positive test. The seven children who tested positive for HSV had a greater response to continuous antiviral therapies (71% CR) than the 13 that had negative or no testing (38% CR), although numbers were small. Seven (16%) patients had NR to one of the continuous antiviral therapies; three (43%) had one or more positive HSV tests and one (14%) had negative HSV studies. There was little difference in response rates to acyclovir and valacyclovir, both intermittent and continuous.

Weston and colleagues' series of 12 children included 9 with recurrent EM.[15] All nine tested positive for HSV through PCR of skin biopsies. The mean number of episodes per year was 2.6.

Siedner-Weintraub and colleagues' series of 30 children included 5 with recurrent EM.[16] Only one had a known cause, with a history of HSV infection but no recent signs of infection. The mean age of these patients was 14.5 years and the mean number of episodes per year was 3.4.

4 | DISCUSSION

Pediatric recurrent EM is a rare condition, with 31 previously reported cases. Our study adds 26 patients to the medical literature and further characterizes the disease. There have been four larger studies of recurrent EM, with a mean age of onset of 25–36.4 years.[1,17-19] Although some children were included in these studies, the data may better represent adult recurrent EM, and we will refer to these studies as the general population. Patient characteristics in our study were similar to those from the literature review of pediatric recurrent EM, but with some notable differences from the general population.

There is a male predominance (70%) in pediatric recurrent EM, but not in the general population (38-55%).[1,17-19] Children had fewer episodes per year (1.8 vs 2.4-6.2).[1,17-19] Hospitalizations were more common in children (33%) than reported by Schofield and colleagues (15%).[1]

The incidence of cutaneous involvement was similar in children (93%) and the general population (90-100%).[1,17-19] In children, there is a higher incidence of oral (84%), genital (30%), and ocular (5%) involvement than in the general population (55-70%, 0-25%, 0%, respectively).[1,17-19] As noted with prior studies, male predominance was seen in children with genital involvement.[4,5,7,8,11-13]

Six patients in our study were initially diagnosed with SJS and hospitalized during the initial outbreak. Weston and colleagues also found two patients originally diagnosed with SJS.[15] Although SJS and EM have similar clinical features, most now recognize that the two diseases are distinct. Early recognition of EM may affect management, such as avoidance of unnecessary hospitalizations and use of antiviral therapy.

The etiology of pediatric recurrent EM has been identified in 47% of cases. HSV was the most commonly identified cause (35%), lower than rates found in the general population.[1,17-19] *Mycoplasma pneumoniae* was the identified cause in 5%, slightly higher than in the general population (0-2%).[1,15,19] It has recently been proposed that *M. pneumoniae*–induced rash and mucositis (MIRM) is a distinct entity, although recurrent MIRM is not described.[20] Two (5%) adolescents had recurrent EM eruptions every 3–4 weeks associated with menstruation.[4]

The wide range of individuals testing positive for HSV across publications can be attributed to the different diagnostic criteria used. Although anti-HSV serum antibodies have a sensitivity of 97% and a specificity of 98%, they are less helpful in distinguishing recurrence of disease because IgM may not be produced during recurrence and IgG remains high indefinitely.[8] HSV cultures of primary infection have a similar sensitivity (97%) and specificity (99%), but the sensitivity is lower (47%) for recurrent infections.[8] HSV PCR is the most accurate technique to diagnose HSV-associated recurrent EM, with a sensitivity of 94% and a specificity of 100%.[8,21] Two studies have investigated the detection of HSV DNA in skin biopsies using PCR in recurrent EM. One study demonstrated HSV DNA in five of eight biopsies in patients with clinical evidence of HSV-associated recurrent EM.[22] Another study found HSV DNA in 6 of 10

TABLE 3 Response to treatment

Treatment	Patients, n (%)	Response to treatment, n			
		Complete response	Partial response	No response	Unknown
Immunosuppressant (intermittent)					
Corticosteroid	17 (65)	14	2	0	1
Antiviral					
Acyclovir	7 (27)	2	2	2	0
Valacyclovir	5 (19)	3	1	0	1
Antibacterial, antifungal (intermittent)	8 (31)				
Clindamycin	2 (8)	2	0	0	0
Azithromycin	2 (8)	1	0	0	1
Cephalexin	1 (4)	1	0	0	0
Nystatin	1 (4)	1	0	0	0
Tetracycline	1 (4)	0	0	1	0
Augmentin	1 (4)	0	0	1	0
Ceftriaxone	1 (4)	0	0	1	0
Antiviral (continuous)	16 (62)				
Acyclovir	9 (35)	2	2	4	1
Valacyclovir	8 (31)	3	2	2	1
Famciclovir	1 (4)	0	1	0	0
Immunosuppressant and anti-inflammatory agents (continuous)	8 (31)				
Dapsone	4 (15)	1	3	0	0
Methotrexate	3 (12)	0	1	0	2
Mycophenolate mofetil	3 (12)	0	1	1	1
Cyclosporine	2 (8)	0	0	2	0
Colchicine	2 (8)	0	1	1	0
Azathioprine	2 (8)	1	1	0	0
Minocycline	1 (4)	0	0	1	0
Fexofenadine hydrochloride	1 (4)	0	0	1	0
Hydroxychloroquine	1 (4)	0	0	1	0

biopsies of HSV-associated recurrent EM and in 6 of 12 biopsies of patients without an identified cause of recurrent EM.[23] These results suggest that even HSV PCR may not be sensitive enough to identify HSV as the cause of recurrent EM in patients with known recurrent HSV and that idiopathic recurrent EM may be due to subclinical HSV infection; thus HSV testing may be of poor utility in pediatric recurrent EM. Despite the aforementioned limitations in testing for HSV, a prospective study with standardized laboratory investigations at times of EM episodes is necessary to better elucidate the etiology of recurrent EM in children.

Treatment of recurrent EM for most patients was challenging. Prednisone has been shown to be efficacious in the treatment of recurrent EM, but its use is controversial and there have not been any controlled studies of its effectiveness.[4] Prednisone may lower the immune response, promoting recurrent HSV infection and further episodes of recurrent EM.[24] A double-blind placebo-controlled trial showed acyclovir to be effective in the treatment of recurrent EM in adults.[25] Although remission of recurrent EM has been reported with antiviral medications with greater bioavailability, such as valacyclovir and famciclovir, in adult cases unresponsive to acyclovir, the results of the aggregate analysis in pediatric recurrent EM suggest little difference.[25-27] The proportion of patients achieving CR with continuous antivirals was similar to those in previous reports in pediatric and general populations. Because HSV is the most common trigger for recurrent EM, HSV testing produces variable results, and antiviral therapy is generally safe and well tolerated, episodic or continuous antiviral treatments may have a role in first-line management regardless of HSV test results.

Recurrent EM in children not responsive to first-line agents may require treatment with immunosuppressant and anti-inflammatory agents. In total, 10 children have received immunosuppressant or anti-inflammatory agents for recurrent EM, with 5 obtaining a CR from dapsone (n = 3), intravenous immunoglobulin (n = 1), and azathioprine (n = 1). Immunosuppressant therapies have been more successful in the general population. Schofield and colleagues' study found CR or PR in 8 of 9 patients with dapsone, CR in 11 of 13 with IVIG, and CR in all 11 with azathioprine.[1]

TABLE 4 Case reports of recurrent pediatric erythema multiforme

Case report	Sex	Age of onset, years	Episodes per year, n	Hospitalizations, n	Disease duration, years	Lesions				Laboratory tests	Treatment	Response
						Cutaneous	Oral	Genital	Ocular			
Arias Santiago et al.[2]	Male	2	1	0	9	X	X					
BaniHani et al.[3]	Male	7	2	0	0.58	X	X		X		Intermittent prednisone	Complete
											Continuous acyclovir	Complete
Bean et al.[4]	Male	11	6	2	17	X	X					
Bean et al.[4]	Female	9	12	8	13	X	X	X				
Bean et al.[4]	Male	13	1	0	3	X	X					
Britz et al.[5]	Male	13	1.25	5	4	X	X	X			Intermittent prednisone	Complete
Chan et al.[6]	Male	6	2	0	0.19	X	X				Intermittent acyclovir	Complete
Grosber et al.[7]	Male	4	0.36	0	7	X	X	X		MP PCR (+), anti-HSV IgM and IgG (−)	Intermittent roxithromycin	Complete
Ladizinski et al.[8]	Male	18	1.5	0	1		X	X		Anti-MP IgG and IgM (+), HSV-1 direct fluorescent antibody (+), anti-HSV IgG (+), anti-HSV IgM (−)	Intermittent prednisone	Complete
											Intermittent azithromycin	Complete
											Continuous valacyclovir	Complete
Messina et al.[9]	Male	10	6	0	3	X				Anti-HSV-1 IgG (+), anti-HSV-1 IgM (−)		
Mittal et al.[10]	Female	2	Unknown	0	19	X	X				Continuous acyclovir	None
											Continuous dapsone	Complete
Mittal et al.[10]	Female	18	2	0	0.5	X	X				Continuous acyclovir	Complete
											Continuous dapsone	Complete
Osterne et al.[11]	Male	11	1.33	0	3	X	X	X		Anti-HSV IgM and IgG (+)	Intermittent acyclovir	Complete
											Continuous acyclovir	Complete
Pope et al.[12]	Male	10	3	2	1	X	X	X		Skin HSV PCR (+), MP PCR (−)	Intermittent acyclovir	Complete
											Intermittent oral steroids	None
Sebastian et al.[13]	Male	7	0.75	1	4	X	X	X		Anti-MP IgG and IgM (+), anti-HSV IgM and IgG (+)	Intermittent intravenous Ig	Complete
Wolf et al.[14]	Male	5	Unknown	0	7	X	X			Skin HSV PCR (−), anti-HSV-1 IgG (+), anti-HSV-1 IgM (−)		
Wolf et al.[14]	Male	7	1.5	0	2	X	X			Skin HSV PCR (−), anti-HSV-1 IgG (+), anti-HSV-1 IgM (−)	Continuous acyclovir	Complete
	82% Male	Median 9	Median 1.5	Median 0	Median 3	94%	94%	41%	6%			

MP, Mycoplasma pneumoniae; PCR, polymerase chain reaction; Ig, immunoglobulin; HSV, herpes simplex virus; CR, complete response; NR, no response.

TABLE 5 Aggregate analysis of current study and literature

Characteristic	Value
Sex, n (%)	
Male	30 (70)
Female	13 (30)
Disease characteristic	
Age at disease onset, years, median (range)	9.1 (0-18)
Episodes per year, median (range)	1.8 (1-11)
Patients requiring hospitalizations, n (%)	14 (33)
Distribution of disease, n (%)	
Cutaneous involvement	40 (93)
Oral involvement	36 (84)
Genital involvement	13 (30)
Ocular involvement	2 (5)
Cause of recurrent EM, n (%)	
Herpes simplex virus	15 (35)
Mycoplasma pneumonia	2 (5)
Menstruation	2 (5)
Epstein–Barr virus	1 (2)
Unknown	23 (53)
Complete response to treatment, n/N (%)	
Intermittent corticosteroids	17/21 (81)
Intermittent acyclovir	5/10 (50)
Intermittent valacyclovir	3/5 (60)
Continuous acyclovir	6/14 (43)
Continuous valacyclovir	4/9 (44)
Continuous dapsone	3/6 (50)
Continuous IVIG	1/2 (50)
Continuous azathioprine	1/2 (50)
Continuous azithromycin	2/3 (67)
Partial response to treatment, n/N (%)	
Intermittent corticosteroids	2/21 (10)
Intermittent acyclovir	2/10 (20)
Intermittent valacyclovir	1/5 (20)
Continuous acyclovir	2/14 (14)
Continuous valacyclovir	2/9 (22)
Continuous dapsone	3/6 (50)
Continuous IVIG	1/2 (50)
Continuous azathioprine	1/2 (50)
Continuous methotrexate	1/3 (33)
Continuous colchicine	1/2 (50)

IVIG, intravenous immunoglobulin.

The limitations of this study include its retrospective design, lack of adequate follow-up for some patients, and variability in examination and treatment. It was difficult to definitively classify treatment response given the episodic and self-resolving nature of EM. There may have been referral bias within our cohort, with refractory cases of recurrent EM being referred to an academic medical center. Similarly, it is likely that referral bias and reporting bias have been a factor in the previously reported case studies of pediatric recurrent EM. These biases may explain the greater proportion of patients requiring hospitalization, the larger portion without an identified etiology, and the low efficacy of antiviral and immunosuppressive agents in all reported cases of pediatric recurrent EM than in recurrent EM in the general population.

In conclusion, our study found that pediatric recurrent EM has a few notable differences from that in the general population. In addition to the predominance of affected boys, there were more hospitalizations, fewer cases caused by HSV, more cases caused by *M. pneumonia*, and a lower response to immunosuppression in children. Pediatric recurrent EM remains a rare disorder, although this study nearly doubles the number of previously reported cases and improves our understanding of this uncommon disease.

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