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CASE REPORT

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Long-term remission in three patients with childhood-onset systemic lupus erythematosus

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Abstract Three cases of childhood-onset systemic lupus erythematosus (childhood SLE) with long-term remission are reported. These cases were not complicated with collagen diseases and had no SLE disease activity index scores either 3 or 5 years after onset. We suggest that some patients with childhood SLE may be able to abandon the maintenance therapy, and that careful observation is needed for each individual case. Uniform remission criteria based on clinical trials are needed.

Key words Childhood · Criteria · Long-term remission · Systemic lupus erythematosus (SLE)

Introduction

The prognosis of childhood-onset systemic lupus erythematosus (childhood SLE) in an earlier series was reported to be worse than that in adults because of the higher frequency of severe renal involvement, central nervous system disease, and infections due to immunosuppression.[1–5] However, the treatment of childhood SLE has fortunately been improved over the past three decades by the introduction of more aggressive therapies such as high-dose steroid therapy,[6,7] and cyclophosphamide pulse therapy.[8,9] In the 1990s, the survival rates have increased to 80%–90% according to several reports,[10,11] although 5- and 10-year survival rates were reported to be about 20%–30% or less in the 1960s.[12]

Many institutes insisted that the major aim of treatment was not only to alleviate the symptoms and signs, control flares, and slow the progression of the disease, but also to gain closer access to the goal of curing the disease.[13]

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However, to date, there have been only a few reports of long-term remission of childhood SLE, and no guideline for bringing about remission of this disease without the use of drugs has been discussed. We describe three cases of childhood SLE in long-term remission.

Case reports (Table 1)

Case 1

A 13-year-old Japanese girl first attended our clinic in September 1983 with a butterfly rash and arthritis, which was later complicated with high-grade fever and oral ulcers. Laboratory tests at admission showed a white blood cell count (WBC) of 3300/mm^3 with 34% lymphocytes, an erythrocyte sedimentation rate (ESR) of 77 mm/h, and a complement-3 (C3) level of 58 mg/dl (normal range 84–151 mg/dl), as well as C4 of 11 mg/dl (normal range 17–40 mg/dl), CH50 of 19.4 IU/ml (normal range 30.0–40.0 IU/ml), antinuclear antibody (ANA) at a dilution of 1:640 (homogenous pattern), anti-DNA antibody of 160 IU/ml (normal range <6 IU/ml), negative anti-SSA/La and anti-SSB/Ro antibodies, negative lupus coagulant, and proteinuria with granular casts. Renal biopsy showed mild mesangial proliferation (WHO class II).

SLE was diagnosed on the basis of the criteria established by the American Rheumatology Association (ARA) in 1985, and oral prednisolone (PSL) therapy was initiated. A few weeks later, all the symptoms and signs subsided, with a marked improvement in the patient's general condition. Laboratory abnormalities had also been normalized. The doses of PSL were gradually tapered, and were then maintained at 10 mg/day until 1992. During the course of maintenance therapy, no flares were observed either in clinical symptoms or in laboratory examinations. In 1992, PSL was tapered further, and was discontinued when the laboratory findings returned to normal, i.e., WBC 5300/mm^3, ESR 5 mm/h, C3 66 mg/dl, C4 13 mg/dl, CH50 30.5 IU/ml, anti-DNA 4.5 IU/ml, and normal urinalysis.

Table 1. Clinical characteristics of the three cases

	Case 1	Case 2	Case 3
Duration of observation (years)	19.0	17.0	11.5
Number of disease flares	0	2	1
C3[a] (mg/dl)	58	66	25
C4[a] (mg/dl)	11	4	3
CH50[a] (IU/ml)	19.4	11.1	10.5
Anti-DNA antibody[a] (IU/ml)	160	160	200
Class stage of WHO[a]	2	4	4
SLEDAI 3 years after onset	0	0	0
SLEDAI 5 years after onset	0	0	0
Concomitant of Sjögren's syndrome	None	None	None
Positive antiphospholipid antibodies	None	None	None

[a] Laboratory data at onset
SLEDAI, systemic lupus erythematosus disease activity index

The patient visited our clinic twice a year for check-ups and to be interviewed regarding her condition. In 2002, at the age of 32, 9.5 years after the termination of PSL, she was found to be healthy, complained of no fatigue, and was working in a bank. In recent laboratory data, the titers of the components of serum complement have been normal and anti-DNA antibody remains absent.

Case 2

A 15-year-old Japanese girl had high-grade fever, butterfly rash, oral ulcers, and arthralgia for 1 month, and in February 1984, she experienced a sudden tonic convulsion followed by unconsciousness. Owing to her abnormal EEG records, including slow waves and slow bursts without spikes, she was transferred from the emergency room to our clinic on suspicion of having SLE. The results of laboratory examinations, which confirmed the diagnosis of childhood SLE, were as follows: WBC, 6800/mm^3 with 41% lymphocytes; ESR, 24 mm/h; C3, 66 mg/dl; C4, 4 mg/dl; CH50, 11.1 IU/ml; ANA, 1:320 (homogenous pattern); anti-DNA antibody, 160 IU/ml; negative anti-SSA/La and anti-SSB/Ro antibodies; negative lupus anticoagulant; massive proteinuria with granular casts. A renal biopsy revealed diffuse glomerular proliferative nephritis (WHO class IV). Her spinal fluid showed no increase in cell numbers or protein levels, and no decrease in glucose levels. Cranial computed tomography showed calcification in the left posterior ventricle.

One course of methylprednisolone (mPSL) pulse therapy (30 mg/kg/day for 3 days) was administered intravenously, and was followed with PSL po. With this treatment, fever, oral ulcers, arthritis, and facial erythema disappeared, and the patient's general condition, including the psychological and neurological signs, improved without any consequences. The oral doses of PSL were tapered gradually, and treatment with 10 mg/day PSL was maintained until July 1997. The patient had flares 1.5 years later, in September 1985. However, the PSL at 10 mg/day po was subsequently discontinued after a gradual decrease. Laboratory examinations yielded the following results: WBC, 6300/mm^3; ESR, 6 mm/h; C3, 83 mg/dl; C4, 18 mg/dl; CH50, 40.3 IU/ml; anti-DNA, 11 IU/ml; negative urinalysis. A second renal biopsy performed in 1999 showed mild mesangial changes (WHO class II) indicating an improvement in her histology. The patient, now 32 years of age, has been well for 5 years without treatment, and all her laboratory data are within the normal range.

Case 3

A 15-year-old Japanese girl with hematuria and facial erythema, followed by high-grade fever, visited our clinic in December 1990. Laboratory findings at admission showed: WBC, 4200/mm^3 with 38% lymphocytes; hemoglobin, 7.4 g/dl; serum iron, 15 μg/dl; ESR, 88 mm/h; C3, 25 mg/dl; C4, 3 mg/dl; CH50, 10.5 IU/ml; ANA, 1:320 (homogenous pattern); anti-DNA antibody, 200 IU/ml; negative anti-SSA and anti-SSB antibodies; negative lupus anticoagulant; hematuria with granular casts. A renal biopsy was performed, and revealed diffuse glomerulonephritis with an active sclerosing lesion corresponding in grade to WHO class IVc. The diagnosis was SLE with severe lupus nephritis on the basis of the ARA criteria of SLE.

Two courses of mPSL pulse therapy were initiated, followed by PSL po and mizoribin, a new immunosuppressive drug developed in Japan. The fever, anemia, and hematuria subsided, and her general condition became normal. The doses of PSL were gradually tapered to 10 mg/day. She had disease flares in December 1991, which were effectively treated by mPSL pulse therapy. Finally, oral PSL was tapered further, and was finally discontinued in May 1999. Laboratory findings then were as follows: WBC, 4800/mm^3; ESR, 14 mm/h; C3, 88 mg/dl; C4, 9 mg/dl; CH50, 38.2 IU/ml; anti-DNA antibody, 8.8 IU/ml; normal urinalysis. A follow-up renal biopsy was performed which showed a histological improvement in the glomerulonephritis (WHO class III grade). No disease flares were detected 3 years after stopping oral PSL administration. Recent laboratory data show that titers of the components of serum complement as well as of anti-DNA antibody are normal.

None of these three patients had experienced pregnancy.

Discussion

We have reported three cases of childhood SLE in long-term remission, which fulfilled the criteria established by the ARA in 1985.[14] They all had the typical symptoms and signs of childhood SLE, as well as hypocomplementemia. These cases were not complicated with collagen diseases, and had no SLE disease activity index (SLEDAI) scores either 3 or 5 years after onset.

In this report, long-term remission in childhood SLE was defined as the maintenance of a complete, treatment-free response for at least 3 years, after which disease-modifying drugs should be stopped. This definition is consistent with the response and remission criteria for adult SLE proposed by Schneider.[15]

The outcome of childhood SLE continues to improve owing to the development of medical care and diagnostic testing. Above all, the improvement in the survival rate over the past few decades is attributed to that fact that the use of aggressive therapies such as steroid-pulse and cyclophosphamide-pulse therapy for childhood SLE became widespread.[11,12] Additionally, in Japan, we have applied those therapies even in cases complicated only with hypocomplementemia, because this condition reflects the disease activity in childhood SLE.[16] In the past, the goals of long-term management in patients with SLE were to suppress the disease activity with a minimum of side effects, and to improve the quality of life in patients with SLE. However, ultimately, it is of course our wish that such patients can, if possible, live without medication. Therefore, it is necessary to distinguish those who can cease the maintenance therapy during the disease course from those who cannot.

There are still no fully established criteria for remission, either in childhood SLE or even in adult SLE, although most rheumatologists probably have their own response and remission criteria based on experience.[15] Since SLE is a heterogeneous, multisystemic disease with a broad phenotype, there are some validated scales that exist just for clinical problems in some individual organs, but randomized controlled trials and longitudinal observational studies of the entire disease are difficult to perform. Additionally, there is a lack of well-defined and measurable outcome parameters in SLE.

Each of our patients underwent a treatment-induced remission, not a spontaneous remission, since in all these cases there was organ involvement and some relapses, and standard treatments for SLE were needed. Previous reports have demonstrated that spontaneous remission was directly related to organ involvement such as renal histology. The frequency of remission in adult patients with SLE was reported to be 2.5%–4%.[17,18] For childhood SLE, we found only a few reports in the literature of long remission without any maintenance therapy. Jacobs[19] reported the case of a 12-year-old girl who had a brief course of low-dose corticosteroid therapy, but no specific therapy later. Glidden et al.[20] reported 17 cases not treated with medication because of minimal to no disease activity, out of 55 patients followed up for 23 years. Buoncompagni et al.[21] reported that medication could be discontinued in one patient only out of 23. However, there is no report that gives details of the clinical characteristics, laboratory data, and renal histology of unmedicated patients. From this viewpoint, we believe that the present report is very important, and is an encouragement to stop medication for SLE.

In conclusion, we suggest that some patients may be able to abandon maintenance therapy, and that careful observation is needed for each individual case. Furthermore, since novel drugs and strategies are being developed not to "cure" but to "improve" SLE, uniform remission criteria based on clinical trials are needed.

References

1. Meislin AG, Rothfield N. Systemic lupus erythematosus in childhood. Analysis of 42 cases, with comparative data on 200 adult cases followed concurrently. Pediatrics 1968;42:37–49.
2. Font J, Cervera R, Espinosa G, Pallares L, Ramos-Casals M, Jimenez S, et al. Systemic lupus erythematosus (SLE) in childhood: analysis of clinical and immunological findings in 34 patients and comparison with SLE characteristics in adults. Ann Rheum Dis 1998;57:456–9.
3. Sandborg CI. Childhood systemic lupus erythematosus and neonatal lupus syndrome. Curr Opin Rheumatol 1998;10:481–7.
4. Gloor JM. Lupus nephritis in children. Lupus 1998;7:639–43.
5. Hashimoto H. Aging and systemic lupus erythematosus. Clin Immunol 1986;18:318–26.
6. Ponticelli C, Zucchelli P, Banfi G, Cagnoli L, Scalia P, Pasquali S, et al. Treatment of diffuse proliferative lupus nephritis by intravenous high-dose methylprednisolone. Q J Med 1982;51:16–24.
7. Silverman ED, Lang B. An overview of the treatment of childhood SLE. Scand J Rheumatol 1997;26:241–6.
8. Valeri A, Radhakrishnan J, Estes D, D'Agati V, Kopelman R, Pernis A, et al. Intravenous pulse cyclophosphamide treatment of severe lupus nephritis: a prospective five-year study. Clin Nephrol 1994;42:71–8.
9. Lehman TJA, Onel K. Intermittent intravenous cyclophosphamide arrests progression of the renal chronicity index in childhood systemic lupus erythematosus. J Pediatr 2000;136:243–7.
10. Lacks S, White P. Morbidity associated with childhood systemic lupus erythematosus. J Rheumatol 1990;17:941–5.
11. Lang BA, Silverman ED. A clinical overview of systemic lupus erythematosus in childhood. Pediatr Rev 1993;14:194–201.
12. Cooks CD, Wedgwood RJP, Craig JM. Systemic lupus erythematosus. Description of 37 cases in children and a discussion of endocrine therapy in 32 of the cases. Pediatrics 1960;26:570–85.
13. Cassidy JT, Petty RE. Systemic lupus erythematosus. In: Cassidy JT, Petty RE, editors. Textbook of Pediatric Rheumatology. 4th ed. Philadelphia: Saunders; 2001. p. 396–449.
14. Watanabe N. A summarization of the clinical studies for children with systemic lupus erythematosus by the Japanese Ministry of Health and Welfare study group: an annual report in 1985. In: Ueta Y, editor. A study for diagnosis and treatment in children with collagen diseases in Japan. Tokyo: Japanese Ministry of Health and Welfare; 1985. p. 9–14.
15. Schneider M. Response and remission criteria for clinical trials in lupus – what can we learn from other diseases? Lupus 1999;8:627–31.
16. Takei S, Maeno N, Shigemori M, Imanaka H, Mori H, Nerome Y, et al. Clinical features of Japanese children and adolescents with systemic lupus erythematosus: results of 1980–1994 survey. Acta Paediatr Jpn 1997;39:250–6.
17. Rowell NR. The natural history of lupus erythematosus. Clin Exp Dermatol 1984;9:217–31.
18. Heller CA, Schur PH. Serological and clinical remission in systemic lupus erythematosus. J Rheumatol 1985;12:916–8.
19. Jacobs JC. Lupus erythematosus with nephritis. Pediatrics 1968;41:369–71.
20. Glidden RS, Mantzouranis EA, Borel Y. Systemic lupus erythematosus in childhood: clinical manifestations and improved survival in fifty-five patients. Clin Immunol Immunopathol 1983;29:196–210.
21. Buoncompagni A, Barbano GC, Pistola V, Fasce L, Micalizzi C, Gusmano R, et al. Childhood systemic lupus erythematosus: a review of 30 cases. Clin Exp Rheumatol 1991;9:425–30.