Paediatric systemic lupus erythematosus: prognostic impact of antiphospholipid antibodies

E. Descloux1, I. Durieu1, P. Cochat2, D. Vital Durand1, J. Ninet3, N. Fabien4 and R. Cimaz2

Objectives. The aim of our study was to investigate the prognostic impact of aPL in paediatric onset systemic lupus erythematosus (p-SLE).

Methods. This retrospective study included 56 patients with p-SLE. χ2-test, Fisher’s exact test, incidence rate ratio and Kaplan–Meier survival curves were used to compare aPL-positive and aPL-negative patients considering the value of SDI (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for SLE) at the end of follow-up, the occurrence of thromboses, organ system involvements and need for immunosuppressive treatment in addition to corticosteroids.

Results. Anti-cardiolipin antibodies and lupus anticoagulants were detected in 27 (49%) and 19 (35%) patients, respectively. These aPL were frequently transient or intermittent (10 and 15 cases, respectively), and only rarely persistent over time (five cases). The risk of thrombosis was significantly higher (odds ratio = 6.42) and occurred earlier in the presence of aPL, especially if aPL were persistent (P < 0.05). The association between aPL and neurological, renal, haematological manifestations or need for immunosuppressive treatment was not statistically significant. After a mean follow-up of 7.2 yrs, 30 patients (54.5%) had an SDI score ≥ 1. The risk of damage (SDI ≥ 1) in aPL-positive patients was three times higher than in aPL-negative patients (P < 0.05). Four of the six fatal cases occurred in the aPL-positive group.

Conclusions. The presence of aPL in p-SLE could represent not only a risk factor for thrombosis but also a poor prognostic factor overall.

Key words: Systemic lupus erythematosus, Paediatric, Anti-phospholipid antibodies, Prognosis.

Introduction

SLE begins in childhood in 10–17% of cases [1–7]. Diagnosis of paediatric onset SLE (p-SLE) is often delayed and symptoms have been reported to be more severe than in adult-onset SLE [1, 2, 5, 7, 8]. Over the last decades, mortality declined remarkably among patients with p-SLE, with 10-yr survival rates exceeding 85% [9]. However, children and adolescents with SLE are now faced with considerable morbidity due to sequelae of disease activity and side-effects of medications [10]. A number of factors have been linked to damage in p-SLE such as cumulative disease activity, medication use or some manifestations at diagnosis like neuropsychiatric symptoms [3, 11–15].

The presence of aPL on two or more occasions at least 12 weeks apart, associated with thrombosis or gravidic complications define the APS [16]. Although APS is rare in childhood [17, 18], frequency of aPL is high in p-SLE, ranging from 19% to 87% (mean 56%) for aCL and from 11% to 62% (mean 31%) for LAC [19]. Manifestations (e.g. neuropsychiatric, renal, haematological) have been reported in aPL-positive children, but the influence of aPL on the disease course remains unclear. The objective of our study was to investigate the prognostic impact of aPL in p-SLE.

Methods

Study population

Medical charts of all patients followed for SLE at the University Hospital of Lyon (France), in paediatric consultation and/or hospitalization units between 1996 and 2006, or in internal medicine, nephrology, rheumatology, dermatology and cardiology units between 2000 and 2006 were reviewed. Fifty-six patients fulfilled the inclusion criteria: (i) onset of SLE symptoms ≤ 16 yrs of age, (ii) at least 4 of 11 classification criteria for SLE [20] and (iii) disease duration ≥ 12 months (except for fatal cases). All patients had been followed regularly. The observation period stopped in June 2006. The design of our work has been approved by the Committee of Protection of the Persons of the Hospices Civils of Lyon, which considered that our study conforms to ethical standards currently applied in France.

Collected data

All data were collected from medical charts and recorded on a standardized data collection form. The 55 patients included in the statistical analysis of prognostic impact of aPL had at least two aPL detections except one patient (one aPL-negative sample) who died of pulmonary embolism secondary to anti-thrombin III deficit, 2 months after SLE onset. One patient was excluded from this statistical analysis as death occurred at day 7, and only one detection was performed (LAC+/aCL–). LAC were detected using international recommendations [21], and aCL were measured by commercial (BioRad–Sanofi Pasteur) or in-house immunoenzymatic assay (enzyme-linked immunosorbent assay). Thresholds of detection were > 12 units IgM phospholipid (UMPL) and > 24 units IgG phospholipid (UGPL) for aCL IgM and IgG, respectively, for samples collected from 2000 to 2006, and > 11 UMPL and > 23 UGPL for aCL IgM and IgG, respectively, for samples collected before 2000. Anti-β2 glycoprotein I were not considered as these aPL were not regularly detected.

Classification according to aPL

Patients were classified in the aPL-negative group (aPL–) if all determinations were negative. In the aPL-positive group (aPL+), we distinguished:

- transient aPL: if detection was positive once or several times, but not confirmed (negative) at 6–12 weeks of interval,
- intermittent aPL: if detection was positive at least twice and confirmed at 6–12 weeks of interval, with period(s) of negative detection,
persistent aPL: if detection was positive at least twice and confirmed at 6–12 weeks of interval, without any period of negative detection.

Statistical analyses

To determine the prognostic impact of aPL, we compared aPL-positive patients vs aPL-negative patients considering the temporal status of aPL. The main outcome measure was the value of SDI (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index or SLICC/ACR for SLE) at the end of follow-up. This score measures the accumulated and irreversible damage in 12 organ systems/domains, ranging from 0 to 47 [10, 22]. Secondary outcomes were occurrence and delay of appearance (since disease onset) of thrombotic events, neurological disorder (epilepsy, cerebral ischaemia, recurrent cephalalgia or migraine), renal disorder (according to the ACR criteria ± chronic renal failure), haematological disorder [anaemia with haemoglobin (Hb) < 10 g/dl and/or thrombocytopenia < 100 g/l] and need for immunosuppressive treatment (in addition to corticosteroid therapy) during the course of SLE.

Data were analysed using S plus software version 6.2 (Insightful). Descriptive statistics were reported as means, standard deviation and medians for quantitative variables, and as frequencies and percentages for qualitative variables. A χ² or a Fisher’s exact test was used to compare aPL-positive and aPL-negative patients. Incidence rate ratio (IRR) and Kaplan–Meier survival curves were considered for thromboses and aPL-negative patients. Incidence rate ratio (IRR) and as frequencies and percentages for qualitative variables. The more frequent organ systems affected (Table 3). After 7.2 ± 0.3 yrs of follow-up, mean SDI score was 1.3 (range 0–7, median 1), and 30 of 55 patients (54.5%) presented damage with SDI ≥ 1. In the aPL+ group, mean SDI score was 1.83 (range 0–7, median 1.5) whereas it was 0.68 in the aPL− group (range 0–5, median 0). In aPL-positive patients, the risk of damage (SDI ≥ 1) was three times as high as in aPL-negative patients (P < 0.05). The more frequent organ systems affected were renal (20%), neuropsychiatric (15%), musculoskeletal and skin (13% each) (Fig. 2).

During follow-up, neurological, renal and haematological disorders were more frequent in aPL-positive patients but not significantly so (Table 3). Nine patients (eight aPL-positive, one aPL-negative) developed chronic renal failure (16%) leading to renal transplantation in three cases. Neurological disorders included cerebral ischaemia (two aPL-positive, one aPL-negative), cerebral sinus venous thrombosis (one aPL-positive), epilepsy (six aPL-positive, two aPL-negative) and recurrent headaches or migraine (seven aPL-positive, two aPL-negative). Almost all patients received corticosteroid therapy (91%; 51/56). Four of the five patients who did not receive corticosteroids were aPL-negative. The addition of an immunosuppressive treatment (66%, 37/56), mostly cyclophosphamide, mycophenolate mofetil or azathioprine, was more frequent in aPL-positive patients, albeit not significant. One-third of patients required admission in an

\[
\text{TABLE 1. aPL types and aPL temporal status in 55 patients with p-SLE}
\]

<table>
<thead>
<tr>
<th>aPL status</th>
<th>LAC−</th>
<th>Transient aPL+</th>
<th>Intermittent aPL+</th>
<th>Persistent aPL+</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aCL−</td>
<td>25</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>28 (51)</td>
</tr>
<tr>
<td>Transient aCL+</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>11 (20)</td>
</tr>
<tr>
<td>Intermittent aCL+</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>12 (22)</td>
</tr>
<tr>
<td>Persistent aCL+</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Total (%)</td>
<td>36</td>
<td>8</td>
<td>15</td>
<td>7 (13)</td>
<td>55 (100)</td>
</tr>
</tbody>
</table>

\[
\text{TABLE 2. Description of six fatal cases of p-SLE}
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<table>
<thead>
<tr>
<th>Sex/age at death (yrs)</th>
<th>Disease duration</th>
<th>aPL status</th>
<th>Causes of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/21</td>
<td>6 yrs (SLE)</td>
<td>Persistent aPL+</td>
<td>Thrombosis (PE)</td>
</tr>
<tr>
<td>M/9</td>
<td>12 yrs (APS)</td>
<td>LAC+/aCL+ (one determination)</td>
<td>Sepsis</td>
</tr>
<tr>
<td>M/17</td>
<td>4 months (SLE)</td>
<td>Persistent LAC+/aCL−</td>
<td>Sepsis</td>
</tr>
<tr>
<td>F/22</td>
<td>11.5 yrs (SLE)</td>
<td>Transient LAC+/aCL+</td>
<td>Severe multisystem SLE flare</td>
</tr>
<tr>
<td>F/15</td>
<td>2 yrs (SLE)</td>
<td>aPL−</td>
<td>Sepsis</td>
</tr>
<tr>
<td>F/16</td>
<td>2 months (SLE)</td>
<td>aPL−</td>
<td>Sepsis</td>
</tr>
</tbody>
</table>

*Pulmonary embolism (PE) secondary to DVT was facilitated by aPL, protein S deficiency and activated C protein resistance. DIC, disseminated intravascular coagulation.

Manifestations during the first month of evolution and during follow-up are summarized in Fig. 1. Six deaths (11%) occurred during follow-up (Table 2). Strikingly, four of the six deceased patients were aPL-positive. The causes of mortality were often multifactorial associating severe SLE flares, infectious complications and thrombotic events.

We compared prognostic impact of aPL considering the SDI value and several manifestations that could be linked to aPL (Table 3). After 7.2 ± 0.2 yrs of follow-up, mean SDI score was 1.3 (range 0–7, median 1), and 30 of 55 patients (54.5%) presented damage with SDI ≥ 1. In the aPL+ group, mean SDI score was 1.83 (range 0–7, median 1.5) whereas it was 0.68 in the aPL− group (range 0–5, median 0). In aPL-positive patients, the risk of damage (SDI ≥ 1) was three times as high as in aPL-negative patients (P < 0.05). The more frequent organ systems affected were renal (20%), neuropsychiatric (15%), musculoskeletal and skin (13% each) (Fig. 2).
intensive care unit (16% in the aPL-negative group vs 40% in the aPL-positive group).

Thirty-one thromboses occurred in 17 patients (14 aPL-positive, three aPL-negative):

- eighteen venous thromboses (16 aPL-positive, two aPL-negative): 14 lower limbs deep vein thromboses (DVT), three pulmonary embolism (secondary to DVT in two cases), one superior vena cava thrombosis, one internal jugular vein thrombosis, one sinovenous cerebral thrombosis.
- Nine arterial thromboses (eight aPL-positive, one aPL-negative): two popliteal thromboses, one internal carotid thrombosis with cerebral embolism, two cerebral ischaemia, two myocardial, one splenic and one renal infarction.
- Four microvascular thromboses (four aPL-positive): three renal microangiopathy, one disseminated intravascular coagulation.

The 14 aPL-positive patients who developed thrombosis presented intermittent aPL in seven cases (two LAC+/aCL−, two aCL+/LAC−, three LAC+/aCL+), persistent aPL in four cases (4 LAC+/aCL+) and transient aPL in three cases (two aCL+/LAC−, one LAC+/aCL−). The interval period between thrombosis and aPL detection was ≤3 months in all cases except one. Odds ratio (OR), IRR and Kaplan–Meier survival curves showed that risk of thrombosis was significantly higher in aPL-positive patients than in aPL-negative patients [OR = 6.42 (1.58–26.11), P = 0.0056; IRR = 4.09 (1.14–22.19), P = 0.0155; Plogrank = 0.0155]. Thromboses were more frequent and occurred earlier if aPL were persistent (Table 3, Fig. 3). All aPL-negative patients who developed thrombosis presented at least one other prothrombotic risk factor: anti-thrombin III or protein S deficiency, prolonged immobilization or smoking (one case each). In contrast, only half of aPL-positive patients with thrombosis presented other prothrombotic risk factor: prolonged immobilization (three cases), smoking and oestrogen/progestative contraception (one case), central catheter (two cases), activated protein C resistance and protein S deficiency (one case). All recurrent thromboses occurred in aPL-positive patients.

Table 3. Prognostic impact of aPL in 55 patients with p-SLE

<table>
<thead>
<tr>
<th>Thrombosis</th>
<th>Neurological disorder</th>
<th>Renal disorder</th>
<th>Haematological disorder</th>
<th>Immunosuppressive treatment</th>
<th>SDI &gt; 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPL− n = 25 (%)</td>
<td>3 (12)</td>
<td>5 (20)</td>
<td>17 (68)</td>
<td>9 (36)</td>
<td>14 (56)</td>
</tr>
<tr>
<td>aPL+ n = 30 (%)</td>
<td>14 (47)</td>
<td>11 (37)</td>
<td>24 (80)</td>
<td>15 (50)</td>
<td>23 (77)</td>
</tr>
<tr>
<td>OR [95% CI]</td>
<td>6.42 [1.58–26.11]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P (χ² test)</td>
<td>0.0056</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Transient aPL n = 10 (%)</td>
<td>3 (30)</td>
<td>5 (50)</td>
<td>9 (90)</td>
<td>5 (50)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Intermittent aPL n = 15 (%)</td>
<td>7 (47)</td>
<td>4 (27)</td>
<td>11 (73)</td>
<td>8 (53)</td>
<td>11 (73)</td>
</tr>
<tr>
<td>Persistent aPL n = 5</td>
<td>4 (80)</td>
<td>2 (40)</td>
<td>4 (80)</td>
<td>2 (40)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>P (Fisher’s test)</td>
<td>0.0077</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Bold values indicate significant P-values (P < 0.05). NS, not significant.

Fig. 2. Distribution of damages considered by the SDI in 55 patients with p-SLE after a mean follow-up of 7.2 yrs.

Fig. 3. Thrombosis-free survival curve in 55 patients with p-SLE.

Discussion

The prognosis of p-SLE has improved considerably in the last decades, but morbidity linked to SLE activity and its treatments remains important [11–15]. In our study, six young patients died. Causes of death were often multifactorial associating severe SLE flares, infectious and thrombotic complications. Therapeutics were heavy as 91% of children received corticotherapy, 66% an other immunosuppressive treatment and 33% required an admission in an intensive care unit. To evaluate SLE severity, we used the SDI score [10, 22], which seemed more representative than SLAM [23] or SLEDAI [24], which only evaluate disease activity at a given time, or area under the curve of SLEDAI-2K, which does not consider morbidity linked to treatments. Ravelli et al. [12] also determined the SDI in 387 patients (mean p-SLE duration of 5.7 yrs) with similar results. The mean SDI score was 1.1 (range 0–10, median 1) vs 1.3 (range 0–7, median 1) in our series. The most frequent damages also affected renal (21.8 vs 20% in our study) and neuropsychiatric systems (15.8 vs 15%). More than half of the patients developed irreversible damage in both studies.

Risk factors of poor prognosis remain controversial in p-SLE. Several studies suggested that morbidity and mortality were higher in male [25, 26] and in non-Caucasian children [1, 26, 27]. In another recent one describing 51 patients with p-SLE, sex and ethnic origin did not influence SDI score, mortality or need for immunosuppressive therapy [13]. Accumulated damages seem strongly associated with disease activity [11, 15] and secondary effects of corticosteroid [11] and immunosuppressive treatments [12, 14]. Neuropsychiatric involvement seems also associated with damage in p-SLE [12]. In the Euro-Lupus cohort (1000 patients comprising 80 patients affected before age 14), main causes of death were SLE activity (26.5%), thromboses (26.5%) and infections (25%) [8]. This study underlined the increased proportion of death linked to thromboses and the strong association.
between aPL and thromboses. However, the specific prognostic value of aPL has been rarely studied.

In our series, more than half of the patients were aPL-positive that is in accordance with the literature [19]. Unlike healthy children, in whom aPL (e.g. LAC, aCL) are usually transient (secondary to common infections) and non-pathogenic [18, 28], aPL were associated with a higher risk of thrombosis and damage in our series. Besides, four of the six deaths occurred in aPL-positive patients. We showed that thromboses were significantly more frequent and earlier in aPL-positive patients than in aPL-negative patients, and that thrombotic risk was correlated with temporal aPL status, increasing with aPL persistence ($P_{\text{logrank}} = 0.0078$). This association between aPL and thromboses is reinforced by the presence of other thrombotic risk factors in only 50% of aPL-positive patients whereas they were present in all aPL-negative patients who developed thrombosis. Moreover, all recurrent thromboses occurred in aPL-positive patients. These results suggest that regular survey of aPL and consideration of aPL temporal status could be useful to evaluate thrombotic risk in patients with p-SLE and to adapt therapeutics. Prospective studies are needed to determine the place of anti-aggregants and anti-coagulants in primary and secondary prevention of thrombotic events in p-SLE. Comparison with previous studies is difficult. Indeed, aPL detection methods are heterogeneous, in part due to the lack of standardization [29]. In studies considering multiple aPL detections, the number of aPL determinations per patient and the time interval between detections are variable or non-specified [30–38]. Several authors also noted aPL titre variation during disease course, that could influence their positivity [30, 32, 33, 35–39] but the temporal variability of aPL positivity was rarely considered. Recently, in accordance with our findings, Male et al. [38] showed that thrombotic events (TEs) were significantly associated with persistent aPL ($P < 0.001$ for LAC, $P = 0.003$ for aCL, $P = 0.002$ for anti-$\beta 2$ glycoprotein I). Persistent (positive on at least two occasions) or transient (positive once) LAC and anti-$\beta 2$ glycoprotein I showed similar strength of association, while aCL were no longer associated with TEs. However, impact of transient aPL was not specifically studied. Like in our study, $\chi^2$-test and Fisher’s exact test were used, but IRR and survival curves considering influence of disease duration on TEs were not considered. However, we did not make distinction between the different aPL subtypes.

Other authors showed a significant association between aPL and autoimmune cytopenia in p-SLE [30, 33, 34], renal [16, 40] or neuropsychiatric manifestations, particularly cerebral ischaemia, epilepsy and migraines [30, 33, 39, 41–45]. In our series, these symptoms were also more frequent in the presence of aPL, albeit not significant. Most of the neuropsychiatric symptoms can be explained by thromboses but aPL could also interfere with extracellular functioning of certain neurotransmitters and conduce to neuronal dysfunction [43]. Lesions of APS nephropathy, resulting from thromboses that affect renal vessels, differ from lesions of SLE nephropathy but they can also alter renal function [16, 40].

Changes in aPL positivity and aPL titre during disease course, SLE flares and remission, and frequent therapeutic changes explain that relation between aPL, disease activity and treatments is difficult to estimate. In our study, most of the children received corticosteroids (91%) and immunosuppressive treatments (66%), both in aPL-negative and aPL-positive groups. As previously reported, we have noted fluctuations in aPL titres during disease course that could influence their positivity [30, 32, 33–35]. Sometimes, the aPL positivity and the increase of aPL titres seemed correlated with SLE flares and inversely, periods of negative aPL detection or the decrease of aPL titres seemed correlated with SLE remission. However, some patients presented high titres of LAC and aCL whatever the disease activity and the therapeutics. Our data do not permit to conclude about the influence of immunosuppressive treatments on aPL. It is difficult to know if aPL fluctuations are cause or consequence of disease activity, or direct effects of therapeutics.

To our knowledge, the influence of aPL in p-SLE outcome as measured by SDI has rarely been studied. We showed that risk of damage (SDI $\geq 1$) in aPL-positive patients was three times as high as in aPL-negative patients ($P < 0.05$) and that SDI score tended to be higher in the presence of aPL. Similarly, Brunner et al. [11] reported that LAC and/or high titre of aCL were a significant predictive factor of damage (SDI $\geq 1$) in p-SLE. In another study, remission rate was significantly lower in aPL-positive patients [37]. Nevertheless, aPL were not correlated with SLE activity or severity measured by ESR, complement C3 levels, SLEDAI and SLAM values. On the contrary, Ravelli et al. [33] showed that aPL were correlated with higher ESR, C3 levels mean values and SLAM. However, these criteria are non-specific and scores such as SLEDAI or SLAM do not allow to evaluate accumulated damages linked to SLE or its treatments. Other studies are needed to confirm that the presence of aPL represents a poor prognosis factor in p-SLE.

Certain limitations in our data preclude generalizations. First, data were retrospective and limited to the region of Lyon; however, information was standardized and recruitment method permitted to describe a representative population of p-SLE. Second, as duration of follow-up was long, methods of aPL detection, number and interval times between determinations were variable. In this, a temporal aPL classification bias remains possible. Third, like in most studies [3, 11–14], we evaluated SDI at the end of follow-up but SDI could be influenced by disease duration [12, 14, 15], and in our series, duration of follow-up tended to be longer in aPL-positive than in aPL-negative patients, albeit not significantly so.

In conclusion, morbidity of p-SLE remains worrisome as 54.5% of children developed irreversible sequelae linked to disease activity and its treatments. Presence of aPL is frequent in p-SLE (55%). Risk of thrombosis was significantly higher and earlier in aPL-positive patients than in aPL-negative patients, and correlated with their temporal status (persistent aPL > intermittent aPL > transient aPL). As the risk of damage (SDI $\geq 1$) was significantly higher in the presence of aPL, these antibodies could represent a factor of poor prognosis overall. Prospective studies are needed to confirm our findings and to determine the place of anti-aggregants and anti-coagulants in therapeutic strategies of p-SLE. An international registry for paediatric APS is currently in place and hopefully will be helpful to elucidate these questions [46].

Rheumatology key messages

- The thrombotic risk in p-SLE was significantly more frequent and earlier in the presence of aPL.
- Risk of damage (SDI $\geq 1$) in aPL-positive patients was three times higher than in aPL-negative patients.

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References

Impact of antiphospholipid antibodies in p-SLE


