Joint Bone Spine 84 (2017) 589–593

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Original article

Familial and syndromic lupus share the same phenotype as other early-onset forms of lupus

Olivia Weill[a], Stéphane Decramer[a], Christophe Malcus[b], Behrouz Kassai[c,d], Isabelle Rouvet[e], Tiphanie Ginhoux[c], Yanick J. Crow[f,g], Frédéric Rieux-Laucat[h], Pauline Soulas-Sprauel[i], Anne Pagnier[j], Isabelle Koné-Paut[k], Maryam Piram[k], Caroline Galeotti[k], Charlotte Samaille[l], Héloïse Reumaux[l], Aurélia Lanteri[m], Sandrine Morell Dubois[m], Hélène Lefebvre[m], Stéphane Burtey[n], François Maurier[o], Aurélia Carbasse[p], Irène Lemelle[q], Ulrich Meinzer[r], Véronique Despert[s], Hugues Flodrops[t], Nicole Fabien[u], Bruno Ranchin[v], Eric Hachulla[m], Brigitte Bader-Meunier[f,g,w], Alexandre Belot[v,*]

[a] *Service de Médecine Interne, Néphrologie, Rhumatologie-hypertension pédiatrique, Centre de Référence des maladies Rénales Rares du Sud Ouest, SORARE, Hôpital des enfants, CHU de Toulouse, 31059 Toulouse, France*
[b] *Service d'Immunologie, Hôpital Edouard Herriot, Hospices Civils de Lyon, 69437 Lyon, France*
[c] *EPICIME-CIC 1407 de Lyon, Inserm, Service de Pharmacotoxicologie, CHU-Lyon, 69677 Bron, France*
[d] *Université de Lyon, Université Lyon 1, CNRS, UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, 69622 Villeurbanne, France*
[e] *Centre de biotechnologie cellulaire et Biothèque, Groupe Hospitalier Est, Hospices Civils de Lyon, 69677 Bron, France*
[f] *Division of Evolution and Genomic Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK*
[g] *INSERM UMR 1163, Laboratory of Neurogenetics and Neuroinflammation Paris Descartes University, Sorbonne-Paris-Cité, Institut Imagine, Hôpital Necker–Enfants-Malades, Assistance Publique-Hôpitaux de Paris, 75015 Paris, France*
[h] *INSERM UMR 1163, Laboratoire d'immunogénétique des maladies auto-immunes pédiatriques, Institut Imagine, 75015 Paris, France*
[i] *CNRS UPR 3572 "Immunopathology and Therapeutic Chemistry"/Laboratory of Excellence Medalis, Institute of Molecular and Cellular Biology (IBMC), Department of Clinical Immunology and Internal Medicine, National Reference Center for Autoimmune Diseases, Hôpitaux Universitaires de Strasbourg, UFR Sciences pharmaceutiques, Université de Strasbourg, 67200 Illkirch-Graffenstaden, France*
[j] *Service de rhumatologie pédiatrique, CHU de Grenoble, 38700 La Tronche, France*
[k] *Service de Rhumatologie Pédiatrique - Centre de Référence des maladies auto-inflammatoires de l'enfant (CeRéMAI), CHU de Bicêtre, APHP, Université Paris-Saclay, Université Paris Sud, 94276 Kremlin Bicêtre, France*
[l] *Unité de Néphrologie Pédiatriques, CHU de Lille, 59000 Lille, France*
[m] *Service de médecine interne, centre national de référence des maladies auto-immunes et systémiques rares, Hôpital Claude Huriez, FHU IMMNeNT, Université de Lille, 59037 Lille, France*
[n] *Centre de néphrologie et de transplantation rénale, Aix-Marseille Université, Assistance publique-hôpitaux de Marseille, France*
[o] *Médecine Interne, Hôpitaux privés de Metz, 57070 Metz, France*
[p] *Service de pédiatrie, CHU Montpellier, 34295 Montpellier, France*
[q] *Service d'Hémato-Onco Pédiatrie, CHRU Nancy, 54511 Vandoeuvre les Nancy, France*
[r] *Service de Pédiatrie Générale, Maladies Infectieuses et Médecine Interne Pédiatrique, Hôpital Robert Debré, APHP, INSERM, U1149, Centre de recherche sur l'inflammation, 75019 Paris, France*
[s] *Service de Pédiatrie Grands Enfants-Adolescents, CHU Hôpital Sud, 35033 Rennes, France*
[t] *Service de Pédiatrie, CHU La Réunion Site de Saint-Pierre, BP 350, 97448 Saint-Pierre, France*
[u] *Laboratoire d'autoimmunité, Service d'immunologie humorale, Hospices Civils de Lyon, CHLS, 69495 Pierre-Bénite, France*
[w] *Service de néphrologie et rhumatologie pédiatrique, hôpital Femme-Mère-Enfant et université de Lyon 1, INSERM U1111, 69677 Bron, France*
[v] *Immunologie et rhumatologie pédiatrique, Hôpital Necker, APHP, 75015 Paris, France*

ARTICLE INFO

Article history:
Accepted 21 September 2016
Available online 28 December 2016

ABSTRACT

Objective: Studies of early-onset systemic lupus erythematosus (SLE) have identified monogenic forms of the disease. The primary objective of this study was to compare the clinical and laboratory features of the first patients included in the GENIAL/LUMUGENE cohort to those reported in previous publications. The secondary objective was to determine whether subgroups with a distinctive pattern of clinical and biological features are seen in predominantly genetic forms of SLE.

* Corresponding author at: Service de néphrologie et rhumatologie pédiatrique, hôpital Femme-Mère-Enfant et université de Lyon 1, INSERM U1111, 57, boulevard Pinel, 69677 Bron, France.
E-mail address: alexandre.belot@chu-lyon.fr (A. Belot).

http://dx.doi.org/10.1016/j.jbspin.2016.12.008

Keywords:
Systemic lupus erythematosus
Monogenic lupus
Pediatrics
Genetics
Autoimmunity

Methods: GENIAL/LUMUGENE is a French nationwide study of the clinical, immunological, and genetic features of juvenile-onset SLE (clinicaltrials.gov #NCT01992666). Clinical and laboratory data from the first 64 patients younger than 18 years who were included in the first part of the study were collected retrospectively. Predefined criteria were used to divide the patients into three subgroups: syndromic SLE ($n = 10$) and familial SLE ($n = 12$) – both presumed to have a strong genetic component – and other forms of early-onset SLE ($n = 42$).
Results: The predefined criteria for identifying subgroups based on knowledge of the clinical and epidemiological features of monogenic SLE showed a significantly younger age at onset in syndromic SLE ($P < 0.05$) and a lower frequency of joint manifestations in familial SLE.
Conclusions: In this study, clinical and epidemiological data alone failed to identify a specific patient subgroup characterized by the same disease presentation or progression. This result may be related to the small sample size or indicate marked heterogeneity of juvenile-onset SLE. Genetic studies using new sequencing techniques in these patients might identify genetic factors responsible for marked phenotypic variability.

1. Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease whose multifactorial pathogenesis involves genetic, immunological, and environmental influences. The first symptoms develop before 16 years of age in 15% of cases [1,2]. Juvenile-onset SLE is characterized by greater severity and a more prominent role for genetic factors, compared to SLE in young adults [3,4]. Over the last decade, studies of early-onset syndromic and familial forms of SLE have led to the identification of monogenetic forms of SLE. The main disease-causing mutations result in complement deficiency, interferonopathies, or apoptosis deficiency [5]. Advances in DNA sequencing techniques will facilitate the identification of these rare mutations.

GENetic & Immunologic Abnormalities in Systemic Lupus Erythematosus (GENIAL)/LUMUGENE (clinicaltrials.gov #NCT01992666) is a clinical study of genetic and immunological abnormalities seen in juvenile-onset SLE. Here, we report the results of the first part of this study, whose primary objective was to compare the clinical and laboratory features of the first patients included in the cohort to those described in previous publications. The secondary objective was to determine whether subgroups with a distinctive pattern of disease progression are seen in predominantly genetic forms of SLE.

2. Methods

We studied the clinical and laboratory features of patients with juvenile-onset SLE who were included in GENIAL/LUMUGENE between December 2011 and August 2015. All patients met the American College of Rheumatology (ACR) criteria for SLE. They were included at 14 pediatric hospitals in France. Starting in 2013, all data were collected prospectively. Earlier data were abstracted retrospectively from the medical records. A tissue bank for immunological and genetic investigations was established. The study was approved by the Sud-Est III ethics committee (#2013-011B), French Data Protection Authority (CNIL, #DR-2013-354), and French Advisory Committee on Healthcare Research Data Processing (CCTIRS, #2013.223).

Inclusion criteria were SLE meeting ACR criteria, disease onset before 18 years of age, coverage by the French statutory health insurance system, and informed consent to study participation.

We defined three patient subgroups based on current knowledge about monogenetic SLE, i.e., symptoms specific of interferonopathies, apoptosis deficiencies, or complement deficiencies; consanguinity; and familial clustering (Fig. 1): syndromic SLE, familial SLE, and other early-onset SLE. Syndromic SLE was defined as the presence of at least one of the following: growth failure in length and weight not explained by drug exposures; intellectual deficiency; birth defects involving the heart, lungs, or kidneys; chilblains; lymphoproliferative disorder; or intracerebral calcifications. Patients with consanguineous ancestry or SLE in a first-degree relative were classified as having familial lupus. All other patients with SLE diagnosed before 18 years of age were classified in the early-onset SLE group.

The following data were collected for each patient: family health history, age at diagnosis, gender, ethnicity, complete list of clinical and laboratory investigations performed during follow-up, and treatments. Disease activity was evaluated by determining the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). At inclusion in the cohort, the following laboratory data were collected: blood cell counts; erythrocyte sedimentation rate (ESR); proteinuria; serum creatinine; total complement (CH50) and C3 and C4 fractions; anti-phospholipid antibodies; auto-antibodies including antinuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA), anti-SSA, anti-SSB, anti-Sm, and anti-RNP. Renal biopsy findings were recorded using the 2003 classification established by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) [6].

Statistical comparisons were performed using Fisher's exact test and the Mann–Whitney test.

3. Results

3.1. Population

We included 64 patients with a median age at the diagnosis of SLE of 12.4 years (1.2–16) and a female-to-male ratio of 4.3:1. The most common past or current clinical manifestations involved the joints (85.9%), skin (79.7%), blood cells (71.9%), and kidneys (43.7%). Renal biopsies were performed in 25 children and revealed a majority of cl IV lupus nephritis (ISN/RPS 2003) with the following distribution: cl II (1pt), cl IIIA (5pt), cl IV-S(A) (2pt), Cl IV-G(A) (7pt), cl IV-S(A/C) (3pt), cl IV-G(A/C) (2pt), cl IV-S(C) (1pt), cl V (7pt), cl VI (2pt). Among them, 5 presented with a combined diagnosis (IV-S(C) + V; IV-G(A/C) + V; IIIA + V; IIIA + IV-G(A); IV-G(A) + V).

3.2. Manifestations in each group

Of the 64 patients, 10 had syndromic SLE, 12 familial SLE, and 42 other forms of early-onset SLE. Manifestations in the syndromic SLE group consisted of growth failure unexplained by drug exposures ($n = 5$), chilblains consistent with interferonopathy ($n = 3$), bone dysplasia ($n = 1$), and intellectual deficiency ($n = 1$). The 12 patients with familial SLE belonged to 10 different families. Among them, 2 had a family history of consanguinity and 10 had an affected