Evidence based recommendations for diagnosis and treatment of childhood-onset systemic lupus erythematosus, including neuropsychiatric lupus – the SHARE initiative.

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Abstract: limit 250 words

Background
Childhood-onset systemic lupus erythematosus (cSLE) is a rare, multisystem autoimmune disorder with significant associated morbidity. Evidence-based guidelines are sparse and management is often based on a clinician's previous experience. In 2012, a European initiative called SHARE (Single Hub and Access point for paediatric Rheumatology in Europe) was launched to optimize and disseminate diagnostic and management regimens in Europe for children and young adults with rheumatic diseases such as cSLE.

Objectives
To provide evidence-based recommendations for diagnosis and treatment of cSLE including neuro-psychiatric lupus.

Methods
Recommendations were generated using the European League Against Rheumatism (EULAR) standard operating procedure. An expert committee, consisting of paediatric rheumatologists from across Europe discussed evidence based recommendations during two consensus meetings using a nominal group technique. Recommendations were accepted if >80% agreement was reached.

Results
A total of twenty-five recommendations were made tackling key approaches to the diagnosis and treatment of cSLE including: eleven for diagnosis, nine on disease monitoring, and five on general treatment. Topics included: appropriate use of SLE classification criteria, disease activity and damage indices; careful assessment of autoantibody profiles; low threshold of suspicion for secondary macrophage activation syndrome; use of hydroxychloroquine and corticosteroid sparing regimens; and the importance of addressing poor adherence. An additional ten recommendations were agreed regarding general diagnostic strategies and treatment indications of neuropsychiatric cSLE.

Conclusions
The SHARE recommendations for cSLE and neuropsychiatric manifestations of cSLE have been formulated by an evidence-informed consensus process to support uniform, high quality standards of care for children with cSLE throughout Europe.

Introduction

Background

Childhood-onset SLE (cSLE) is a severe, chronic, systemic autoimmune disease that impacts significantly on the child or young person affected. cSLE shares its disease pathogenesis with adult-onset SLE, but cSLE generally has a more severe clinical phenotype. This is reflected overall by a higher disease activity at disease onset, and throughout the disease course. Organ systems such as the kidneys and the central nervous system (CNS) are more often involved in cSLE, and patients accrue more damage over time. Long term use of corticosteroids is common (1-4).

cSLE is rare, and this low prevalence makes clinical research challenging, resulting in a significant paucity of evidence-based data and subsequent guidelines for disease management. Consequently, the management of patients with these cSLE differs widely between countries including across Europe (5). Treatment approaches can vary between clinicians even within centres. Decisions are made often based on adult-derived trials or studies, anecdotal evidence based on published case series in children, and individual clinician experience. To foster equity of access to the highest standards of care and uniformity of practice, evidence-based international guidelines are therefore urgently needed.

To achieve this, collaboration between countries is necessary: only by sharing expertise can we optimise and disseminate best practices regarding diagnosis and management of cSLE and its related clinical manifestations. For this reason, the Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) project was initiated (6). One of the key objectives of this project was to provide guidance regarding best practices for the diagnosis and management of children with rheumatic diseases (PRD), including cSLE.

Methods

A European-wide panel of 16 experts in paediatric rheumatology was established to develop evidence-informed recommendations. A project plan for the systematic literature search was written following the EULAR standardised operating procedure of recommendations (7).

Systematic literature search and study selection

A systematic literature search, based on specific research questions was performed in the electronic databases PubMed/MEDLINE, EMBASE and Cochrane databases in July 2013 (Figure 1). The search was limited to English articles from 1970 onwards. Case series with a minimum of 3 patients were included. Articles including patients over 18 years of age were only included if they include data on 3 or more patients younger than 18, and if this group was analysed separately. A validated filter was used for both domains, to specifically select articles on children and adolescents only. The filter was adapted for cSLE to exclude neonates, as neonatal lupus was beyond the scope of the review. All synonyms of cSLE were searched in MeSH/Emtree terms, title, and abstract; and reference tracking was also conducted for all included studies (full search strategy including inclusion/exclusion criteria in online supplementary figure S1).

Validity assessment

Two reviewers (NG and NdG) independently screened all titles and abstracts according to the predefined inclusion and exclusion criteria. Only articles dealing with either original research or meta-analyses were included. If necessary, the full text was checked to determine eligibility. A third reviewer (SK and/or MWB) resolved discrepancies regarding article inclusion; agreement was reached in all cases.

Articles fulfilling inclusion criteria were then sent to a panel of seven European cSLE experts (MWB, SK, TA, AR, IKP, BBM, CP); two experts reviewed all articles independently. They assessed level of evidence and methodological quality of the papers (8, 9) and extracted the data using adapted classification tables for epidemiologic, diagnostic (10) and therapeutic (11) studies. Data extraction was done using predefined data extraction forms. If there were any discrepancies, a third expert was asked to give a final assessment.

Establishment of recommendations

The results of the literature review were mapped against the *a priori* research questions, and provisional recommendations for the diagnosis and treatment of cSLE were formulated (by NG, NdG, SK, MWB) based on this evidence. When no literature in children could be found to map against a particular recommendation, adult literature was consulted. These were presented to the expert committee (n=15) in web-based surveys. The expert committee (TA, BBM, PB, PD, IKP, PL, LM, SO, CP, AR, AvR, YU, NW, SK, MWB) completed these surveys (100% response rate) and gave their opinions on the statements. Recommendations were revised according to responses to the surveys and discussed at two sequential face-to-face consensus meetings in March 2014 (Genova, number of experts participating, n=15; moderators: BF and AR) and March 2015 (Barcelona, n=14; moderator: BF).

To reach consensus, the nominal group technique (NGT) was used, in which equal participation from group members is ensured (12). At least 80% of the experts had to agree with a recommendation for it to be accepted. This process resulted in a set of prioritised final recommendations.

Results

Figure 1 summarizes the results of the literature search. A total of 9,341 articles were identified and reviewed regarding treatment and management of cSLE. After screening on title and abstract and assessing the full text for relevance, 126 articles fulfilled the inclusion criteria. Fifty articles relating to diagnosis and management of cSLE generally, and 24 articles to neuropsychiatric manifestations of cSLE were scored by the experts. Articles pertaining to lupus nephritis informed a specific set of complimentary recommendations published separately in view of extent and complexity.

The meetings resulted in 25 recommendations pertaining to the diagnosis and treatment of cSLE in general (Table 1) and 10 for neuropsychiatric cSLE (Table 2).

Recommendations regarding diagnosis of cSLE

Prompt, accurate diagnosis of cSLE is crucial to enable timely initiation of appropriate treatment, including multi-disciplinary care. However, there are no validated diagnostic criteria for cSLE. Despite some differences regarding symptoms at onset, pattern of organ involvement, and severity of disease between cSLE and adult-onset disease, their similarities mean that the established ACR classification criteria for SLE are widely used for cSLE (3, 13). In 2012, new classification criteria for SLE were been published and to date, two studies have assessed the performance of these SLICC classification criteria for SLE in children (14-16). Both found that although some specificity may be lost, the SLICC criteria did have better sensitivity than the ACR-criteria (14-17). Therefore, the panel agreed that the SLICC-criteria can be used, evidence to date indicates they may well be preferable in cSLE, and should be used to aid referral to, or at least consultation with a paediatric rheumatologist. Similarly, they may help prompt referral, even if a child does not yet meet full criteria, since these are classification criteria and not diagnostic criteria.

A hallmark of SLE is the presence of autoantibodies, particularly those directed towards nuclear autoantigens. Next to ANA, autoantibodies including anti-dsDNA, anti-Sm, anti-RNP, anti-

Ro/SSA, and anti-La/SSB antibodies (collectively these epitopes are referred to as 'ENA' (Extractable Nuclear Antigens)) are prevalent in cSLE: dsDNA 54%-93%; anti-RNP 22%-50%; anti-Sm 17%-52%; anti-Ro/SSA 33%-54% Anti-La/SSB 14%-32% (18-25). As such, including all of these antibodies in the diagnostic work up of cSLE was strongly recommended. However there are no diagnostic antibodies with specific predictive qualities (e.g. disease severity, organ involvement, age of onset) despite extensive efforts to find them (26-34). Notably, patients negative for anti-dsDNA antibodies and/or ENA can still be diagnosed with cSLE.

Hereditary complement deficiencies can predispose to lupus or lupus-like disease at an early age. Early recognition of these deficiencies should facilitate adequate treatment of disease and comorbidities including infections, which are especially important as these patients seem to have a higher mortality (35, 36). Therefore, screening for complement deficiencies via CH50 and AP50 (or other validated classic and alternative complement pathway assay) is important in cSLE, especially in young lupus patients. It was also recognised that there are other causes of monogenic lupus outside of the complement pathway, thus normal complement screening assay results do not preclude this possibility.

Recommendations regarding cardiopulmonary involvement in cSLE

Although frequently considered unusual in cSLE, cardiac and pulmonary involvement does occur, but often this can be asymptomatic initially (37-45). Respiratory symptoms or signs such as exertional intolerance could be an indication towards pulmonary or cardiac pathology. However there is a wide differential diagnosis that must be considered and use of appropriate diagnostic procedures should be performed to find out whether cardiopulmonary involvement is due to cSLE.

Early recognition of cardiopulmonary involvement is important when trying to prevent subsequent organ damage. Therefore a baseline screen in every cSLE patient for cardiopulmonary involvement is advised. Additionally, intermittent monitoring for any future progression or new involvement of these organ systems over time can be considered, as it is not clear how many children with asymptomatic cardiopulmonary involvement become symptomatic.

Macrophage Activation Syndrome (MAS)-related recommendations

Macrophage activation syndrome (MAS) is a rare but severe, potentially life-threatening complication of cSLE, characterized by liver insufficiency, coagulopathy, pancytopenia, and neurologic symptoms (46, 47). Patients can develop MAS at any time during their disease. Distinguishing sepsis from MAS can be difficult, as they may share features such as fever, cytopenias and hepatic involvement, both resulting in disseminated intravascular coagulation and systemic inflammation. There are differences, as for example in MAS ferritin levels tend to increase dramatically, whereas hyperferritinaemia is generally more modest in sepsis (48, 49). A bone marrow aspirate (BMA) should be performed to assess the cause of cytopenias and to detect possible hemophagocytosis. This will help in making a diagnosis of MAS. As MAS can be rapidly progressive and life threatening, the threshold for diagnostic procedures should be low. However, if the patient is clinically unstable, treatment should not be delayed for BMA purposes alone. Classification criteria for MAS in systemic Juvenile Idiopathic Arthritis have been developed, and could be helpful in SLE as well (50).

Recommendations for monitoring and general management of cSLE

The frequency of visits to the paediatric outpatient clinic is dependent on clinical presentation as well as the age of the patient. Visits should be regular, especially at diagnosis and after flares and a basic set of investigations is recommended for each visit. The recommended

frequency of visits as well as the important clinical parameters that should be checked at each visit is similar to the recommendations for adult-onset disease (51, 52). The exception to this is the addition of regular height and weight monitoring for the paediatric population. Children with cSLE can develop growth impairment which can be difficult to subsequently catch up and may eventually lead to a lower final height due to continuous disease activity and/or corticosteroid use. Pre-pubertal and peri-pubertal patients receiving a high cumulative dose of corticosteroids are specifically at risk for growth impairment, which must be proactively looked for (53, 54).

It is strongly recommended that disease activity and disease damage should be regularly and comprehensively assessed using standardized tools to monitor disease progression. Many tools are available for this purpose (55). For example, disease activity can be monitored with the British Isles Lupus Assessment Group index, as it has been validated for use in children (56) and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Disease damage should also be comprehensively assessed annually, for example using the paediatric version of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (pSDI) (53).

A broad range of ocular manifestations including retinopathy or optic nerve disease can occur in cSLE. Additionally, two of the most commonly used drugs for SLE, glucocorticoids and hydroxychloroquine, can affect the eyes (57-59). Therefore, it is recommended that patients have access to the expertise of paediatric ophthalmology. Paucity of evidence regarding ophthalmological risks due to long-term glucocorticoids and hydroxychloroquine use means that annual examination of the eyes should be considered in the paediatric age group (60).

Despite minimal published evidence supporting the benefits of sunlight-protection in cSLE patients, sunscreens are widely recommended to prevent photosensitive rashes and as part of general disease management. One study in eleven adult SLE patients showed that some, but not all types of sunscreen prevented the development of UV-radiation induced skin lesions (61).

Adolescent patients need to be carefully supported and prepared for transfer of their care to the adult services once they reach adulthood. During adolescence patients need to develop self-management skills and become responsible for their own health. For example, patients need to learn to recognize and manage their symptoms, schedule their own appointments, adhere to treatment and necessary life-style modifications to keep their disease under control (62-65). One of the major challenges during the transitional process is non-adherence to treatments (63, 66), this should be addressed frequently at out-patient clinics. EULAR guidelines for the transitional process in young people with rheumatic diseases have been recently published to support professionals in designing a coordinated transition programme that should improve the long-term outcomes of this vulnerable group of patients. [REF….. SK: revised version has already been re-submitted, so hopefully publication will follow soon].

General recommendations on treatment of cSLE

It is recommended that all children with lupus should be on hydroxychloroquine (HCQ) routinely. A systematic review of 95 articles analysing the beneficial and adverse effects of antimalarial therapies such as HCQ in adults with SLE showed a broad spectrum of beneficial effects, such as a higher remission rate, less relapses and less accrual of damage. Additionally, HCQ has a favourable safety profile (67). Adult studies show that long-term use of HCQ is relatively safe, although the risk of retinopathy increases with the increasing cumulative dose (67). Unfortunately, no such evidence is available for children with cSLE, but studies in patients with juvenile idiopathic arthritis show that doses up to 6 mg/kg/day (based on lean body weight) are safe to use (68).

Lack of adherence has been associated with a higher disease activity and more damage (69-71). Rates of non-adherence can be high as 50% and disease severity does not guarantee

medication adherence (72). Therefore, adherence should be checked whenever a patient shows poor response to a treatment, measuring medication (trough) levels may be helpful to detect non-adherence. When a patient experiences side effects from a drug, choice of therapy will need to be reassessed and switched if necessary. If it is established that compliance to oral prednisone and HCQ is adequate, yet disease activity means that tapering of oral prednisone is not possible, addition of a DMARD is recommended in order to improve disease control and permit subsequent corticosteroid tapering

The use of rituximab has been described in five studies to date including a total of 59 children with cSLE. All patients had acute, life threatening symptoms or symptoms that did not respond to standard treatment. Two dose regimens were described, which both proved to be effective and safe in the majority of the patients (73-77).

Recommendations on the diagnosis of neuropsychiatric SLE

Neuropsychiatric cSLE (NP-cSLE) can be a common manifestation of lupus in children (78-84). To promote uniformity and comparability between NP-SLE manifestations in children and adults, it is recommended that the ACR nomenclature and case definitions for NP-SLE (85) are also used in cSLE. As is the case in adult-onset NP-SLE, no single clinical, laboratory, neuropsychological or imaging test can be used in children to differentiate NP-cSLE from other causes of neuropsychiatric manifestations. There have been some small studies aimed at trying to identify specific biomarkers or imaging techniques for neuropsychiatric involvement in cSLE, but large, controlled studies are lacking (86-98). Therefore, the recommendation regarding the diagnostic evaluation of neuropsychiatric symptoms is adopted from the adult EULAR guidelines (99, 100).

It is important to make a detailed and thorough assessment of any patient with suspected NP-SLE. In the context of a suspected NP-cSLE diagnosis or worsening of neuropsychiatric disease, an initial comprehensive work up should include all other potential underlying causes, including infections, hypertension, metabolic abnormalities or adverse effects of medication. The type of neuropsychological symptoms and signs will also guide the overall diagnostic approach.

Importantly, not all NP-SLE manifestations can be detected with conventional MRI-imaging techniques. In addition, conventional MRI (as well as more novel MRI imaging modalities) may reveal findings of uncertain clinical relevance, and/or of dubious specificity for cSLE or CNS manifestation from other cause. Formal neuropsychiatric testing can be used to ascertain the presence of neurocognitive dysfunction, but these tests can be time-consuming, costly and difficult to interpret. A helpful screening tool for neurocognitive dysfunction in cSLE is the Pediatric Automated Neuropsychological Assessment Metrics (Ped-ANAM) which is now available. Non-specialists can use the tool in a relatively short amount of time, in order to screen patients for possible neurocognitive dysfunction (101). This and other, similar tools are recommended to screen for possible problems in this area.

Recommendations on the treatment of NP-cSLE

The evidence for the treatment of NP-cSLE in children is especially limited. Recommendations are therefore based principally on adult guidelines for the management of NP-SLE (100), adapted for use in children by the expert panel. It was noted that this remains an important area for future clinical research. When non-SLE related causes for neuropsychiatric symptoms or signs are excluded, glucocorticoids and immunosuppressive therapy are indicated (100).

Recurrent seizures in SLE may benefit from epilepsy treatment. However, one single seizure without evidence for epileptic activity on electroencephalogram (EEG) in the brain is usually not

an indication for epilepsy treatment. Undertaking a careful evaluation seeking and treating the underlying cause(s), including anti-inflammatory treatment of potential NP-cSLE, and/or control of hypertension (if present) most often suffices to prevent further seizures.

Discussion

A total of 35 recommendations for diagnosis, management and treatment for cSLE and NP-cSLE in children have been formulated by the cSLE working party of SHARE. All recommendations were accepted with >80% agreement.

These recommendations are intended to help specialists with decisions regarding the general care for children with cSLE. When following the recommendations, the most severe symptom(s) or sign(s) should guide treatment decisions. For example, when a patient suffers from mild haematological involvement as well as severe neuropsychiatric disease, the latter should guide the treatment of choice. Notably, recommendations regarding the management of nephritis in cSLE will be published separately.

It must be noted that good quality evidence regarding diagnosis and treatment in children with cSLE specifically is limited. Therefore, the expert panel refrained from being too specific regarding diagnostic procedures, monitoring intervals or specific drug treatments due to lack of robust evidence underpinning some statements. This emphasises the need for more research on diagnostic procedures, as well as treatment in this population. International collaboration will be vital, as large cohorts are difficult to achieve.

In conclusion, the SHARE project has resulted in recommendations on diagnosis, management and treatment of cSLE and NP-cSLE, based on best available evidence and expert opinion. These recommendations should facilitate the optimization of the management of this rare disease.

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