Comorbidity in young patients with juvenile systemic lupus erythematosus.

How can we improve management?

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Developments in research leading to better diagnosis, treatment and ultimately improved long-term outcomes for children and adolescents with juvenile systemic lupus erythematosus (JSLE) in the last decades has increased clinicians' awareness of the role of holistic care in patient management. JSLE is a complex systemic disease associated with chronic inflammation with potential impact on many aspects of health and quality of life of young people. It is widely recognised that JSLE is associated with a higher rate of co-occurrence of other medical conditions (1, 2), some directly related to the disease or treatment, and some reported as a detection artefact, as many of these patients are subjected to multiple clinical appointments and medical investigations. There is evidence that co-existent physical or mental conditions in children and adolescents negatively affect patient outcomes, irrespective of the type of illness (3, 4) and require complex management associated with increased health-care costs (5).

Comorbidity versus multimorbidity

Comorbidity is defined by the concomitant presence of one or more noncommunicable illnesses in addition to a primary medical condition (index disease). The term *comorbidity* was coined in 1970 by Alvan Feinstein, an American epidemiologist who investigated patients with rheumatic fever and other medical conditions, and made significant contributions to improved chronic disease classification and the development of the field of clinical epidemiology (6). Although historically, the focus of recognising and managing comorbidity was directed towards populations of increased age, because of an interdependent relationship between age and illness, it is increasingly recognised that comorbidities can affect people of any age.

Comorbidity and *multimorbidity* are considered interchangeable terms, especially in the context of approaching patient management from a secondary and tertiary care perspective, which is usually centred around a disease index. In contrast, the term *multimorbidity* is more patient-centric implying focus on a holistic and multi-disciplinary management approach, highly suitable in the context of a multi-system autoimmune disease such as JSLE (7).

Age impact on comorbidity prevalence in general population

Comorbidity in young people is understudied overall, despite increased awareness of the epidemiological transition of the age onset for various chronic diseases (8). Worrying statistics from the US estimate that one in 5 children have obesity and that the prevalence of type 2 diabetes is estimated to increase by 4-fold by 2050 among people younger than 20 years of age (9). Although historically cardiovascular disease (CVD) and cardiovascular risk (CVR) are actively assessed in mature/older populations, recent research estimates that 1-3% children in the US have hypertension, while stroke is one of the top 10 causes of death during childhood (10). There is also evidence of increased associations of various physical and psychological illnesses in children and adolescents (11).

There are similarities between various processes involved in ageing and their related comorbidities and emerging research suggests that they could be targeted simultaneously for health benefits (12). In addition, the recognised link between chronic inflammation and comorbidity, irrespective of age or underlying condition (13-15), can offer hope that targeted disease management from a younger age can address the life-long comorbidity risk.

Systemic lupus erythematosus (SLE) as index disease, and its impact on comorbidity risk and health care costs

It is widely accepted that patients with SLE are at increased risk of developing certain comorbidities, including CVD, stroke, osteoporosis, and infection (16, 17), with recent guidelines recommending monitoring risk factors for these conditions and instituting preventative treatment in patients with both juvenile (JSLE) and adult-onset SLE (18, 19).

We know that adults with SLE are five times more likely to suffer from comorbidity compared to the age-matched general population (20), due to a combination of factors, such as disease activity, medication, and socioeconomic factors. The burden of comorbidity is significant in adults with SLE, with one study reporting that more than fifty percent of SLE patients reported three or more physical comorbidities (21).

Comorbidities are frequently associated with more complex patient management needs, poorer prognosis, and increased health care costs in adult-onset SLE (22, 23). The cost of care of children with JSLE is even higher, with one study reporting that 11% of care costs are directed towards dialysis, reflecting the high burden of renal comorbidity in younger patients (24).

What is different about comorbidity prevalence in JSLE compared to adult-onset SLE?

JSLE patients have increased prevalence of renal and neuropsychiatric involvement and almost 6 times increased standardised mortality rate compared to patients with adult-onset SLE (25). A high proportion (44.2%) of children with JSLE develop irreversible damage only 3.8 years from diagnosis, suggesting a high risk for accumulating comorbid illnesses early in life, however there is a lack of research looking specifically into the prevalence of overall comorbidities in JSLE. The most common JSLE related damage is associated with kidney disease, scarring alopecia and cognitive impairment (26).

CVD is probably the most studied comorbidity associated with JSLE. Children with JSLE are estimated to have 100-300-fold CVD-related increased mortality compared to age-matched young controls (27). In addition, JSLE patients are younger at the time of first CVD event (usually myocardial infarction) compared with patients with adult-onset SLE (28). Subclinical atherosclerosis can be associated with both traditional and non-traditional CVR factors in this patient population (29), suggesting an increased risk for CVD comorbidity from early age. More than one in three patients aged 10-21 years

recruited to the Atherosclerosis Prevention in Paediatric Lupus Erythematosus (APPLE) study (investigating treatment with atorvastatin for atherosclerosis prevention in JSLE) had hypertension (30), while a recent large cohort study of adults with SLE estimated its prevalence at 24.6% (21). Dyslipidaemia was also found to be more common in JSLE than in adult-onset SLE (21, 31), while the prevalence of obesity was comparable (21, 32). One in 5 children with JSLE had osteoporosis (33), which is more than reported in adults with SLE in a recent meta-analysis (34). Despite striking evidence that the comorbidity risk associated with JSLE is likely higher than that of adult-onset SLE, there is almost no research directed towards stratifying and managing JSLE patients based on their comorbidity index.

Unmet needs for better JSLE patient stratification, comorbidity assessment and management

Recent efforts for JSLE patient stratification based on biomarkers for organ involvement bring hope for future patient-tailored and more effective treatment approaches (35), and ultimately better comorbidity prevention and management. Improved health and long-term outcomes for children and adolescents world-wide are recognised as public health priorities.

JSLE patients have an increased comorbidity risk compared to matched young healthy controls but there are differences within JSLE cohorts as they are highly heterogeneous. Patients with early onset JSLE have higher mortality and neuropsychiatric/vascular/cutaneous damage despite similar frequencies of severe cumulative manifestations (36), and they should be monitored more closely.

From an early age, children and adolescents with JSLE already acquire various CVR factors, such as hypertension, elevated triglycerides, apolipoprotein B, haemoglobin A1c and insulin levels, as well as increased arterial stiffness, in addition to non-traditional CVR, such as elevated homocysteine and fibrinogen, when compared to matched healthy controls (37). The key for adequate comorbidity management is the appropriate patient stratification for tailored interventions. Recent research identified lipid biomarkers, which enabled JSLE patient stratification based on their atherogenic lipid profile (38)**,** while immunological and metabolic signatures of JSLE patients can help predict long-term outcomes and CVR (39, 40). Furthermore, there is evidence that targeted therapeutic interventions to address the increased comorbidity risk in JSLE could be beneficial and acceptable to young patients. A dietary intervention in girls with JSLE stratified based on their lipid profile was associated with benefit (41), providing evidence that diet could be a suitable strategy for improving JSLE CVR profile in selected categories of patients. A tailored 3-month aerobic exercise programme in physically inactive children with JSLE ameliorated their cardiorespiratory capacity/autonomic function, and therefore their physical comorbidity (42).

What can we do better?

Recent UK-led international collaboration efforts into implementing “treat to target” recommendations in JSLE have been met with enthusiasm from young patients and their parents (43), raising hope that some of the excessive comorbidity risk affecting these young patients could be managed in the future through tighter disease control. However, primary prevention and education is likely to have a significant role in managing children and adolescents’ health overall, and the increased comorbidity risk in JSLE. Many JSLE biomarkers require further validation in ethnically and geographically diverse cohorts before implementation in clinical practice. The complex adolescent physiology and behaviour account for the under-recognised and inadequately managed gender-bias affecting the comorbidity risk of young people, as well as their attitudes to health interventions (44, 45). The future may bring more standardised ways to assess comorbidities in young people in general, and JSLE in particular, and even a disease-focused comorbidity index to guide clinical management.

There is also hope for more efficient and better targeted treatments for JSLE, with minimal toxicity. Finally, we must let young people's voice be heard and involve them in the long journey for better health in JSLE through efforts to align clinician and patient priorities.

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