PAEDIATRIC RHEUMATIC DISEASE

Phenotype and prognosis of juvenile systemic lupus erythematosus

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Cases of systemic lupus erythematosus with onset during childhood seem to be more severe than adult-onset disease, possibly because of genetic influences. But is more-detailed information about the molecular heterogeneity of the disease needed in order to tailor treatments and improve prognosis?

Refers to Ambrose, N. *et al.* Differences in disease phenotype and severity in SLE across age groups. *Lupus* http://dx.doi.org/10.1177/0961203316644333 (2016).

Whether systemic lupus erythematosus (SLE) in children is more severe than adult-onset disease is still debated, although most evidence seems to indicate that this is the case. A large study from the UK that directly compared the phenotype and severity of SLE across age groups supports the view that paediatric-onset SLE has an aggressive phenotype and poor outcomes[1]. In a broader sense, however, the findings highlight the need for precise phenotyping and individualized treatment for patients with SLE regardless of age at onset.

SLE predominantly affects women of reproductive age, but up to ~20% of cases have an onset in childhood. Unlike other paediatric rheumatic diseases, juvenile-onset SLE is largely similar to its adult counterpart. In fact, the disease has the same clinical manifestations in childhood and in adulthood, and the same classification criteria are used for SLE in children and adults; however, the incidence of organ involvement seems to be different and the disease severity worse in paediatric cases.

Ambrose *et al.*[1] analysed the effect of age at onset of SLE on the clinical phenotype of SLE in two large cohorts, together comprising 413 patients with juvenile-onset and 511 with adult-onset disease. Several other studies have dealt with the presentation of SLE in different age groups — in particular with respect to the incidence of nephritis, a hallmark of severe disease — and mostly found that early disease onset was associated with a more severe phenotype. However, substantial heterogeneity exists among the different reports, as case and age definitions varied, and cohorts were frequently small owing to the rarity of the disease. Hence, the study by Ambrose *et al.*[1], being the largest direct comparison of juvenile and adult-onset SLE to date, brings an important advancement in current knowledge.

The authors not only compared juveniles and adults, but also subdivided the cohort into age groups: <12 years, 12–18 years and >18 years. Although it is not clear how the adults were selected for the study, overall the proportion of males was higher in juveniles (age ≤18 years) than in adults (17% versus 8%). The female predominance of the disease is indeed already known to be less prevalent in childhood.

Whereas the prevalence of skin rash was no different across all age groups, nephritis was more common in juveniles than in adults (44% versus 33%, $P = 0.001$), although the gap was smaller when biopsy-proven nephritis was considered (31% versus 27%). Diffuse proliferative glomerulonephritis was the most common type of nephritis in all age groups. Young patients underwent biopsy much earlier, on average; this raises the question of how soon this procedure should be performed, and whether the histological results could have been influenced by an earlier or later biopsy. Our practice, as at most other centres, is to perform a renal biopsy in children and adolescents who display any kind of persistent urinary abnormality or other evidence of unexplained possible renal involvement (for example, hypertension and/or elevated serum creatinine level).

Thrombocytopenia and haemolytic anaemia were also more prevalent in the children than in the adults, a finding that has already been reported by others. On the contrary, the prevalence of neuropsychiatric lupus, another dreadful complication of the disease, did not differ between juveniles and adults. Of note, the standardized mortality ratio was almost six-fold higher in juveniles than in adults; this finding is worrisome and deserves further study. The contribution of antiphospholipid antibodies to disease expression was not mentioned in this paper but certainly can be a contributing factor to organ damage.

Other papers, including results from a national registry[2] and a meta-analysis[3], have evaluated the differences between SLE in children and adults. The subject has been well summarized in a review by Mina and Brunner[4]. Most[5,6], but not all[7], studies found a higher incidence of nephritis in the paediatric groups. Others have examined the phenotype of paediatric SLE according to the age at onset[8], but results regarding damage and disease activity according to age have been inconsistent.

The impression that seems to emerge from most of these studies, of paediatric-onset SLE being more severe, is not easily explained. Genetic influences have been suggested to have a major role; indeed, it is now known that some forms of lupus-like disease or of very early onset disease (in the first years of life) can actually be of monogenic aetiology[9]. These forms of disease usually display a prominent interferon signature, just as 'standard' SLE does, but interestingly the phenotype is quite different.

Now, all of the data discussed above are important, but they have little relevance from a practical point of view as any paediatric rheumatologist provides care on the basis of clinical needs, regardless of a patient's age at disease onset. Much more important would be to find good predictors of poor prognosis, in order to identify patients who should be treated aggressively before the development of organ damage. Also, because SLE is clinically heterogeneous, coupling the different phenotypes to biological characteristics would enable the formation of more homogeneous groups; such groupings would be ideal for performing clinical trials, which have often been unsatisfactory to date, both in juvenile and adult-onset SLE. In this regard, a major breakthrough was made by longitudinally profiling the blood transcriptome of a large group ($n = 158$) of paediatric patients with SLE[10]. Personalized immunomonitoring uncovered individual correlates of disease activity that enabled stratification of the patients into seven groups. Of note, distinct signatures were found in different classes of nephritis (proliferative versus membranous).

With regard to disease prognosis, major improvements have been made in the recent past in the paediatric form of SLE. Earlier diagnosis, the use of more appropriate treatments (including aggressive immunosuppression when needed), and an improved approach to managing and preventing disease complications have led to decreased mortality and improved quality of life. However, the increased life expectancy of patients with juvenile-onset SLE has brought new problems that were not so important in the past, such as premature atherosclerosis and osteoporosis, and issues related to female fertility and sexuality (such as contraception and pregnancy). For atherosclerosis, atorvastatin is currently being evaluated in clinical trials; for low bone mass, vitamin D supplementation and, in severe cases, bisphosphonates are useful options. Nonetheless, and paradoxically, cumulative damage can progressively increase despite improved disease control. Moreover, long-term immunosuppression may also add toxicity to the disease burden, and last but not least the psychological consequences of such a chronic disease can be devastating, especially in adolescents.

> "paediatric-onset SLE has an aggressive phenotype and poor outcomes"

In conclusion, it seems that juvenile-onset SLE is more aggressive than its adult-onset counterpart. However, and more importantly, immunomonitoring can dissect the heterogeneity of the disease and help to form more homogeneous patient groups, so that a tailored follow-up and treatment is made possible.

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Competing interests statement
The author declares no competing interests.