Comparison of juvenile and adult onset systemic lupus erythematosus

Systemic lupus erythematosus is a multisystem autoimmune disease of unknown aetiology, described as juvenile systemic lupus erythematosus if the onset is before 16–18 years of age. This review outlines current understanding of juvenile systemic lupus erythematosus and differences between this and adult onset disease.

Systemic lupus erythematosus is a multi-system autoimmune disease of unknown aetiology, which appears heterogeneous in pathogenesis, clinical presentation and manifestation. Definitions of juvenile systemic lupus erythematosus vary, describing the onset of systemic lupus erythematosus before either 16 or 18 years. A paucity of studies into juvenile systemic lupus erythematosus has historically meant extrapolation of adult research and management. For example, the revised American College of Rheumatology Classification Criteria from 1997 (*Table 1*) were created as a standardized diagnostic tool for adults with systemic lupus erythematosus, and have since been validated in juvenile disease (Ferraz et al, 1994; Hochberg, 1997). However, there are still no standardized guidelines for management of systemic lupus erythematosus of any age of onset. This is likely related to the heterogeneity of disease, which has become more complex as evidence suggests that juvenile systemic lupus erythematosus differs significantly from adult disease.

This review outlines current understanding of epidemiology, pathogenesis, clinical manifestations, prognosis and management of juvenile systemic lupus erythematosus. It also highlights the differences between juvenile and adult onset disease, which spur on researchers to address issues such as more severe disease activity, higher chronic disease burden and higher rates of non-adherence to therapies in juvenile systemic lupus erythematosus.

Table 1. Revised American College of Rheumatology criteria for classification of systemic lupus erythematosus

1	Malar rash	Fixed erythema, flat or raised, over the malar eminences
2	Discoid rash	Erythematous circular raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur
3	Photosensitivity	Exposure to ultraviolet light causes rash
4	Oral ulcers	Includes oral and nasopharyngeal ulcers, observed by physician
5	Arthritis	Non-erosive arthritis of two or more peripheral joints, with tenderness, swelling or effusion
6	Serositis	Pleuritis or pericarditis documented by electrocardiography or rub or evidence of effusion
7	Renal disorder	Proteinuria >0.5 g/d or 3+, or cellular casts
8	Neurological disorder	Seizures or psychosis without other causes
9	Haematological disorder	Haemolytic anaemia or leukopenia (<4000/litre) or lymphopenia (<1500/litre) or thrombocytopenia (<100 000/litre) in the absence of offending drugs
10	Immunological disorder	Anti-double-stranded DNA, anti-Sm and/or antiphospholipid
11	Antinuclear antibodies	An abnormal titre of antinuclear antibodies by immunofluorescence or an equivalent assay at any point in time in the absence of drugs known to induce antinuclear antibodies

Any combination of four or more of 11 criteria, well documented at any time during a patient's history, makes it likely that the patient has systemic lupus erythematosus (specificity and sensitivity are 95% and 75% respectively). From Hochberg (1997), American College of Rheumatology (1999)

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Epidemiology and demographics

Between 15 and 20% of cases of systemic lupus erythematosus occur in those under the age of 16 years (Tucker et al, 1995). The incidence of juvenile systemic lupus erythematosus in America has been reported to be 0.3–0.9 per 100 000 children-years, with prevalence of 3.3–8.8 per 100 000 children (Kamphuis and Silverman, 2010). The adult prevalence of systemic lupus erythematosus varies between 40 and 200 cases per 100 000 individuals, depending on ethnicity (Johnson et al, 1995). The median age of onset is 12.6 years (Watson et al, 2012) whereas that of adult onset disease is around 33 years (Hoffman et al, 2009).

The female predominance remains with age, although the female:male ratio is lower in childhood than adult onset. Up to 20% of juvenile systemic lupus erythematosus patients are male (Lo et al, 1999) and males are younger at diagnosis (*Table 2*) (Watson et al, 2012).

Ethnicity seems to influence the frequency and severity of clinical manifestations and response to therapies. As in adults, juvenile systemic lupus erythematosus occurs more frequently in black, Hispanic, native American and south-east Asians. African-American patients with systemic lupus erythematosus appear to have younger age of onset and increased frequency of incidence of systemic lupus erythematosus and renal disease, although there is conflicting evidence on the effects of Hispanic ethnicity on outcomes for juvenile systemic lupus erythematosus.

Pathogenesis

Systemic lupus erythematosus appears to have complex, multi-factorial aetiology, still not fully elucidated. There is the 'waste disposal' hypothesis in systemic lupus erythematosus, where there are abnormalities in the normal clearance of apoptotic material. This apoptotic material may be immunogenic in those predisposed to autoimmunity, which may lead to a 'break of immunotolerance', the development of autoantibodies to a variety of intracellular nuclear antigens and hence to the development of autoimmune disease (Walport, 2000). Characteristically, immune-complex deposition in organs occurs, giving rise to a variety of clinical manifestations. However, it remains unknown whether the mechanisms of autoimmunity differ and if so, to what extent, between juvenile and adult onset systemic lupus erythematosus.

Also unclear is why the peak incidence of onset of juvenile systemic lupus erythematosus is during adolescence, with median age of onset about 12.6 years. Hormonal factors have long been suspected as important in systemic lupus erythematosus, with clear female predominance, probable increased frequency of disease flare in pregnancy and the observation that systemic lupus erythematosus tends to 'burn out' by the menopause.

Puberty and adolescence incorporates vast flux of physical, social and neurocognitive development. The latter has been discovered to be associated with ongoing grey matter changes in the pre-frontal cortex in the developing adolescent and young adult brain (Blakemore and Choudhury, 2006). More research is required to elucidate the normal pubertal process, let alone that in disease states such as systemic lupus erythematosus, where neuropsychiatric involvement, including cognitive impairment, occurs more frequently in juvenile than adult onset disease (Yu et al, 2006).

Socioeconomic factors, particularly educational status, have, at least in adults, influenced adherence with therapies and thus potential disease outcome (Koneru et al, 2008). Similar studies in children and adolescents are lacking.

The genetic predisposition to systemic lupus erythematosus is variable and as reviewed by Deng and Tsao (2010), a number of different HLA haplotypes and single nucleotide polymorphisms have been described in systemic lupus erythematosus, many of which vary according to ethnic origin. However, these genetic studies have not attempted to differentiate between adult and childhood onset systemic lupus erythematosus.

However, the UK Juvenile Systemic Lupus Erythematosus Cohort Study (a large, multicentre, collaborative, national juvenile systemic lupus erythematosus inception cohort) has shown a strong family history of autoimmunity, with 38% of patients having more than one autoimmune disease in the family, 15% of which was systemic lupus erythematosus, perhaps suggesting genetic factors are important in the pathogenesis of juvenile systemic lupus erythematosus (Webb et al, 2011; Watson et al, 2012).

Clinical features that differ in juvenile *vs* adult onset systemic lupus erythematosus

Diagnosis of systemic lupus erythematosus can be difficult at any age, perhaps more so for juvenile systemic lupus erythematosus, as symptoms can be non-specific and some clinical features can manifest years before others. Between 40 and 90% of patients with juvenile onset disease have undifferentiated, non-specific symptoms which do not fit the American College of Rheumatology criteria for systemic lupus erythematosus. Hence an 'index of suspicion' is recommended if patients do not meet the American College of Rheumatology criteria at presentation.

The UK Juvenile Systemic Lupus Erythematosus Cohort Study published detailed phenotypic data on 232 patients from 14 centres across the UK over 4.5 years, which are consistent with data from other juvenile cohorts as regards epidemiology, organ involvement, disease activity and damage (Watson et al, 2012).

The few existing juvenile systemic lupus erythematosus cohort studies have shown that renal, haematological and neuropsychiatric disease tends to be more frequent, acute and severe in juvenile onset *vs* adult onset systemic lupus erythematosus (Tucker et al, 1995, 2008; Font et al, 1998; Hersh et al, 2009; Hoffman et al, 2009).

Differences in other clinical features are less clear. Musculoskeletal disease appears frequently (60–82%), rashes occur in 40–60%, scarring alopecia is notable (10%) and systemic upset (unexplained fever, fatigue, malaise, weight loss) is common in juvenile systemic lupus erythematosus (40–90% of cases) (Font et al, 1998; Carreno et al, 1999; Watson et al, 2012).

The relative frequency of gastroenterological, respiratory and cardiovascular manifestations compared to adults with systemic lupus erythematosus has not been conclusively elucidated in large cohort studies.

Case reports suggest a higher prevalence of more uncommon manifestations of systemic lupus erythematosus in children, such as intestinal vasculitis and pancreatitis, with significantly increased prevalence

Table 2. Key differences between juvenile and adult onset systemic lupus erythematosus

	Juvenile onset	Adult onset
Gender	Female:male 5.6:1	Female:male 9:1
Clinical features	Higher frequency: renal, haematological, neuropsychiatric, intestinal vasculitis (rare), pancreatitis (rare)	Higher frequency: alopecia, arthritis, cardiovascular, gastrointestinal, discoid rash, Raynaud's phenomenon, respiratory
Serology	Higher frequency: anti-Sm, anti-ribosomal P, anti-neuronal, +/- anti-double stranded DNA, low C3	Same frequency: anti-nuclear antibody
End-stage renal disease	15–20%	10–15%
Lupus nephritis classification	Class IV most frequently	Class IV most frequently
Chronic damage rate	50–60%	40%

of biopsy-confirmed smooth muscle antibody-positive autoimmune liver disease predating disease onset in 9.8% of juvenile systemic lupus erythematosus patients *vs* 1.3% of adults (Irving et al, 2007). However, the degree of difference in manifestations between juvenile and adult onset disease is not clearly defined. Comparisons of large, well-characterized cohorts of juvenile and adult onset systemic lupus erythematosus patients are needed.

Renal

Lupus nephritis is the primary manifestation in 60–80% of juvenile systemic lupus erythematosus patients and remains the most significant determinant of prognosis and mortality. Adults with systemic lupus erythematosus have a lower incidence (37–52%) in the few direct comparison studies (Brunner et al, 2008; Hersh et al, 2009).

Juvenile systemic lupus erythematosus nephritis has a worse prognosis than in adults – more juvenile patients than adults require dialysis (19% *vs* 5.7%) (Tucker et al, 2008). Relapse rates for lupus nephritis are also higher in juvenile systemic lupus erythematosus patients (between 35 and 45%) compared to 20–32% of adult patients (Mok, 2006; Chen et al, 2008; Gibson et al, 2009). African-American ethnicity confers a significantly higher risk for progression to end-stage renal failure, independent of age of onset of systemic lupus erythematosus.

Pereira et al (2011) retrospectively compared renal and patient survival in paediatric patients over 3 decades. Median age at diagnosis was 12.3 +/- 2.9 years. They found that nephrotic proteinuria at diagnosis imparted a poor prognosis and increasing proteinuria correlated with progression of renal disease. They also stratified patients into four 'eras' according to the introduction of the primary immunosuppressive drug. Most significantly, they found that addition of mycophenylate mofetil improved 5-year renal survival from 52% to 91% and overall patient survival from 83% to 97%. However, there are no prospective trials directly comparing mycophenylate mofetil to cyclophosphamide for the treatment of lupus nephritis of juvenile onset, as exist for adult onset.

Neuropsychiatric

Neuropsychiatric manifestations are likely more common in juvenile systemic lupus erythematosus than adult onset, with reported prevalence ranging from 26 and 95%. Within the first year of diagnosis, 70% of children develop features compatible with neuropsychiatric systemic lupus erythematosus compared to only 28% of adults (Hoffman et al, 2009). Psychosis appears more common in juvenile disease, with 7.5–12% frequency according to the few studies performed, in contrast to 2% prevalence in 30-year follow up of 500 adult systemic lupus erythematosus patients (Pego-Reigosa and Isenberg, 2008). Seizures, unilateral chorea and focal cerebrovascular deficits (not always associated with positive antiphospholipid antibody status) are also predominant manifestations of juvenile onset neuropsychiatric systemic lupus erythematosus.

Neuropsychiatric systemic lupus erythematosus is difficult to diagnose and treat at any age. Although the American College of Rheumatology (1999) describes 19 syndromes comprising neuropsychiatric systemic lupus erythematosus for adults, there are no core validated neuropsychiatric criteria for juvenile disease. Symptoms wax and wane and there are no specific or sensitive, validated, diagnostic serological (blood or CSF) tests, imaging or standardized neuropsychometric tests.

Treatments for neuropsychiatric systemic lupus erythematosus at any age are non-specific and limited, and symptoms may take up to 6 months to acquiesce despite therapy. Psychosis secondary to glucocorticoids is not clearly differentiated from neuropsychiatric systemic lupus erythematosus and creates another barrier to compliance.

Studies have shown significant differences between healthy controls and patients with neuropsychiatric systemic lupus erythematosus, using functional brain magnetic resonance imaging combined with validated neuropsychometric tests. Attention, verbal fluency and working memory (executive/higher brain functioning) are impaired in those with neuropsychiatric systemic lupus erythematosus and have been mapped to altered activity in fronto-parietal and pre-frontal motor cortex, hippocampus and limbic regions of the brain (DiFrancesco et al, 2007).

Brain structure continues to evolve from childhood to the mid-20s. Synapses are 'pruned' during adolescence, after a period of synaptogenesis which peaks at 2 years old and occurs again to a lesser extent in puberty. After a peak in early adolescence, grey matter decreases with age, corresponding to synaptic pruning. Pruning is thought to lead to fine-tuning functional networks, influenced by individual experience (Blakemore and Choudhury, 2006).

The functional balance between cognitive control and emotional centres appears important and altered in adolescence. It has also been suggested that adolescents are driven to seek more extreme incentives to compensate for low recruitment of motivational brain circuitry, (Bjork et al, 2004) which may partially explain the altered risk/reward behaviour and decision making which we inherently associate with 'teenage' behaviour.

Research is hampered by the heterogeneity of clinical manifestations of neuropsychiatric systemic lupus erythematosus of any age, costly and invasive nature of investigations, and the difficulty of controlling for ethnicity, socioeconomic and educational status. Cognitive development of executive brain function also continues throughout adolescence and thus it is perhaps unsurprising to see such wide variation in reported figures for neuropsychiatric disease in children.

Haematological

Up to 91% of patients with juvenile systemic lupus erythematosus have haematological manifestations, although compared to adult onset disease, neutropenia is not as common as thrombocytopenia, lymphopenia and anaemia. Secondary antiphospholipid syndrome in juvenile

disease appears to be associated with a higher frequency of venous (60% *vs* 32%) and arterial (32% *vs* 15%) thrombosis (Avcin et al, 2008) and neurological complications (chorea in 14% *vs* 1%) than adults. Adults tend to have more livedo reticularis, heart valve and pulmonary hypertension manifestations (Cervera et al, 2002).

Comparison of antiphospholipid syndrome in children and adults is complicated by the fact that the classification criteria for antiphospholipid syndrome (Miyakis et al, 2006) include recurrent miscarriages, hence the frequency of thrombosis is skewed towards children.

Serological differences

Antinuclear antibodies (ANA) (part of the American College of Rheumatology classification criteria) are almost always present in juvenile systemic lupus erythematosus. The prevalence of autoantibodies and association with clinical manifestations seems higher in juvenile systemic lupus erythematosus for anti-ribosomal P, anti-neuronal, antiphospholipid (about 36%) and anti-Sm antibodies (22–32%) and perhaps for anti-double stranded DNA (dsDNA) antibodies (69–73%) (Ferraz et al, 1994; Watson et al, 2012). Anti-dsDNA and anti-Sm perhaps confer higher risk of renal and neuropsychiatric systemic lupus erythematosus (Jurencak et al, 2009), but the full significance of presence and titre of the other autoantibodies, including ANA, is still not elucidated for adults, let alone in juvenile systemic lupus erythematosus.

As for adults, the absence of lupus-associated autoantibodies is not necessarily associated with a better prognosis. 'Seronegative' patients can develop clinical features which meet American College of Rheumatology criteria for severe manifestations, e.g. neuropsychiatric systemic lupus erythematosus or lupus nephritis, without the presence of typical serology.

The presence of autoantibodies such as ANA and dsDNA can also vary throughout the life of an individual with systemic lupus erythematosus, so may require periodic re-evaluation. However, only anti-dsDNA and complement 3 (C3) levels appear to correlate to disease activity to some extent, but not for all clinical manifestations. Hence clinical judgement and surveillance are important for the management of patients with systemic lupus erythematosus of any age of onset.

Outcome and prognosis

Although 5-year survival rates have significantly improved from 30% to 90% over the last few decades for systemic lupus erythematosus of any age of onset, the frequency of cumulative disease damage seems higher in children than adults. Disease duration and activity are the most important predictors of damage in both adult and juvenile disease and strong predictors of early morbidity and mortality (Alarcon et al, 2001). Approximately 50–60% of patients with juvenile systemic lupus erythematosus have evidence of impairment of organ systems within 5 years, as seen in two American retrospective cohort studies (Chalom, 2004; Hersh et al, 2009). The UK Juvenile Systemic Lupus Erythematosus Cohort Study found disease-associated damage in 28% of patients with a median 4.5-year follow up, with predominance of neurological disease damage (8%), of which 3% had experienced one or more cerebrovascular accidents. They also found that 4% had renal damage manifesting predominantly as persistent heavy proteinuria (Watson et al, 2012).

The Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index (SDI) was developed to measure irreversible, cumulative damage that has occurred since diagnosis of systemic lupus erythematosus (Gladman et al, 1996). Although the SDI was designed for adult systemic lupus erythematosus, it has been validated for use in juvenile disease (Brunner et al, 2002). Some studies have used SDI to report predictors for damage accrual in juvenile systemic lupus erythematosus, other than disease duration and activity over time (Bandeira et al, 2006; Tucker et al, 2008). These include presence of major organ involvement, early and major disease flares, and use of immunosuppressive medications and/or cumulative corticosteroid treatment. Male sex and non-white ethnicity have not been consistently associated with poor outcome in juvenile systemic lupus erythematosus (Kamphuis and Silverman, 2010). Therefore, true long-term survival rates and predictors of long-term outcomes in juvenile systemic lupus erythematosus are not clear.

Some adult systemic lupus erythematosus studies show that poorer outcomes are associated with younger age and poor adherence, reinforcing the need for more research into juvenile systemic lupus erythematosus (Koneru et al, 2008; Daleboudt et al, 2011). Non-adherence, reported in up to 30% of adult patients, has been associated with higher morbidity, hospitalization and poor renal outcome. Cognitive functioning and concerns about adverse effects of medication were strong predictors of non-adherence in this study, which is of particular interest for the adolescent systemic lupus erythematosus group, with known higher incidence of neuropsychiatric involvement, together with possibly heightened psychosocial factors which could affect decisions to take medications or attend clinics.

There are limited data on psychosocial and quality of life outcomes for patients with juvenile systemic lupus erythematosus. In the two American studies quoted earlier, 89–95% of patients completed high school and 55–85% had either started or completed college. However, about 20% of patients in both cohorts were not working. Short-Form 36 Physical Component Scale (SF-36 PCS) scores were also significantly lower for patients with juvenile systemic lupus erythematosus than the national mean in the Chalom (2004) cohort.

Longer term studies are needed to determine whether secondary morbidities, such as the increased cardiovascular risk seen with adult systemic lupus erythematosus, are shared with juvenile disease. Similarly, osteoporosis and osteonecrosis, which have reported prevalence in juvenile

systemic lupus erythematosus of 7–20% and 5.4–23% respectively, are of particular concern, given that growth, long-term bone survival and function may be affected, but limited research exists to elucidate the impact.

Management and challenges

Pharmacological

Management of systemic lupus erythematosus of any age of onset is limited by paucity of the clinical trial evidence base. No specific medication has been approved for juvenile systemic lupus erythematosus.

Therapies remain largely anecdotal, and carry potential toxicity and long-term risk. High doses of glucocorticoids are often used in severe systemic lupus erythematosus. Glucocorticoid-related weight gain, mood changes, low bone mineral density, striae and acne are of particular concern to teenagers. The recommendation is, where possible, to use the smallest dose for the shortest time.

It is not clear whether ovarian protection should be offered with cyclophosphamide therapy for severe renal and neuropsychiatric systemic lupus erythematosus or not, as there is less risk of infertility in girls and adolescents than adult women or males with systemic lupus erythematosus (Silva and Brunner, 2007).

Hydroxychloroquine is used for systemic lupus erythematosus of any age. Mycophenylate mofetil has improved renal survival and appears useful for haematological and dermatological features. Problems with pharmacokinetics and body-surface-based dosing may lead to under-dosing in those with juvenile disease.

B cell depletion therapy (anti-CD20 monoclonal antibody: rituximab), although not yet of proven benefit in the few, adult only, randomized clinical trials, has improved various clinical manifestations in both children and adults, including renal disease, in preliminary studies.

In general, intravenous therapy is preferred in juvenile systemic lupus erythematosus than in adults to increase adherence, which otherwise can be a real issue.

Belimumab, a monoclonal antibody that inhibits B-cell activating factor, has been approved for adult systemic lupus erythematosus (excluding renal and neuropsychiatric systemic lupus erythematosus) but its efficacy in juvenile disease has yet to be investigated.

Non-pharmacological

A multidisciplinary approach by specialists in adolescent systemic lupus erythematosus is crucial, as recommended by Brunner et al (2011). They highlight the importance of adherence to medications and clinic visits, as well as self-management training (Koneru et al, 2008; Duvdevany et al, 2011). Physical therapy, psychological support and dietary services should also be incorporated. Few UK centres have a tertiary or quaternary adolescent rheumatology service incorporating a multidisciplinary team.

The importance of adherence to therapy and follow-up in clinics is highlighted by the fact that non-adherence is one of the most frequent contributors to poor renal outcome and incidence of chronic renal damage in systemic lupus erythematosus (Sun et al, 2011; Houssiau, 2012).

Smoking, alcohol, recreational drug use and ultraviolet exposure (known triggers or perpetuating factors for disease activity, or factors contributing to poor adherence) also present challenges in adolescents with systemic lupus erythematosus and hence should be addressed.

A careful and individualized plan of transition into adult care is crucial. This has been shown by seminal work by Janet McDonagh, who is currently a lead for the STEPP project (supporting transitions for young people with life-limiting conditions). Transition needs to incorporate physical, psychosocial, educational and vocational needs of the developing adolescent and emerging adult (Jordan and McDonagh, 2007; McDonagh, 2007). Transition also needs to be a real consideration in the planning of health services, given the significant number of adolescents in rheumatology clinics who need follow up into adulthood for chronic diseases such as systemic lupus erythematosus.

Conclusions

Up to one in five systemic lupus erythematosus patients present under the age of 16 years. Juvenile systemic lupus erythematosus currently presents a challenge at every stage of management for various reasons. It appears to be associated with more frequent and severe renal, haematological and neuropsychiatric involvement than adult onset disease, with a significantly larger burden of chronic organ damage. The aetiopathogenic mechanisms underpinning these differences are not understood. The impact of damage is not clear because of a lack of long-term studies, although it is suspected to reduce long-term physical and psychosocial function and outcome. Pharmacological therapies for juvenile systemic lupus erythematosus are limited by this lack of evidence, as extrapolation of adult studies to juvenile patients is too simplistic. New well-defined cohort studies provide hope for more understanding of juvenile systemic lupus erythematosus and its long-term outcomes. **BJHM**

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KEY POINTS

About 15–20% of systemic lupus erythematosus patients have disease onset under the age of 16 years. Juvenile systemic lupus erythematosus is variously defined as onset before 16 or 18 years.

Pathogenesis of juvenile systemic lupus erythematosus is unknown.

Nephritis is the primary manifestation in 60–80% of juvenile systemic lupus erythematosus patients and a key predictor of morbidity and mortality.

Neuropsychiatric systemic lupus erythematosus is commoner in juvenile systemic lupus erythematosus, in particular cognitive impairment, psychosis, seizures and chorea.

Poor adherence to therapy is a problem at any age, perhaps more so in adolescence.

Chronic damage is more common in juvenile systemic lupus erythematosus than adult onset disease.

A multidisciplinary approach is required to deliver comprehensive, individualized care, acknowledging physical and psychosocial needs of juvenile systemic lupus erythematosus patients, with careful transition into adult services paramount.