Pathogenesis of neurocognitive and neuropsychiatric manifestations in childhood-onset lupus: an overview

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Abstract

This review explores current understanding of neuropsychiatric systemic lupus erythematosus (NPSLE) of childhood onset, in particular neurocognitive impairment. As yet, fewer studies have focused on childhood onset NPSLE compared to adult onset NPSLE and diagnosis still involves the 1999 American College of Rheumatology case definitions of neuropsychiatric syndromes, which were developed for adults. Although a validated core set of neuropsychometric tests exist for childhood onset NPSLE, these still have limitations and possible biomarkers and newer neuroimaging modalities remain mostly experimental. Important differences exist between childhood and adult onset SLE and specifically with NPSLE, outlined in this review. Normal adolescent brain development also involves significant differences from adults, particularly in executive function and social cognition. These issues may impact on the pathogenesis of NPSLE during this vulnerable period and also influence their management options.

Introduction

Neuropsychiatric systemic lupus erythematosus (NPSLE) remains an enigma. There are several reasons why the pathogenesis and treatments of NPSLE remain in general poorly defined and understood.

NPSLE which includes neurocognitive impairment is a relatively common manifestation in both adult and childhood onset lupus. However in children, NPSLE is probably more common and more severe, with some studies reporting a prevalence rate of up to 95%.[1-5] However, many studies have reported widely varying figures on the prevalence of NPSLE in both adults and children. The heterogeneity of this clinical subset of SLE complicates elucidation of its pathogenesis. Part of the reason for this heterogeneity is due to a lack of uniformly accepted clinical criteria for NPSLE. In an attempt to standardize definitions, 19 distinct neuropsychiatric syndromes of SLE, as identified by a working party on behalf of The American College of Rheumatology (ACR) in 1999 were defined and are tabulated in Table 1.[6] However, these ACR case definitions of NPSLE have not been validated for use in children and adolescents, further limiting current research in this distinct age group of patients.

Further uncertainty exists, as no consistent pattern of cognitive impairment has emerged in adults with SLE.[7] Cognitive impairment is thought to be independent of disease duration, disease severity or medication use, but studies have not consistently controlled for this in either adult or childhood onset SLE.

This review outlines the difference between childhood and adult onset SLE. It also describes more specifically neuro-psychiatric and neuro-cognitive manifestations, and describes recent advances that provide insights into the normal development of the adolescent brain, which appear fundamental to the understanding of the pathogenesis of neuro-cognitive impairment in this age group. The pathogenesis of NPSLE in general, and more specifically relating to childhood onset SLE, is explored in relation to the involvement of autoantibodies, cytokine and other mediators. In addition we outline how neuroimaging elucidates anatomical, metabolic and functional neurological abnormalities. We also consider the current paucity of genetic studies in NPSLE, in particular childhood onset SLE. Finally, we outline the few therapeutic options that currently exist for NPSLE of both adult and adolescent onset.

Differences between childhood and adult systemic lupus erythematosus

Several differences between childhood onset and adult SLE exist. Around 15% of patients with SLE develop lupus as a child (≤16 years of age). The median age of onset of childhood onset SLE is around puberty.[8] There is also a higher frequency of males with SLE at childhood than adult onset, with ratios of 5.6 to 1, *versus* 9 to 1 (female to male), the significance of which is not yet understood.[9,10] Childhood onset SLE often presents with more acute and severe disease features than adult SLE based on studies providing direct comparisons,[11,12] as reviewed previously.[13,14] Childhood onset SLE has a higher frequency of renal, neurological, and hematological involvement than adult SLE at the time of diagnosis,[8,11,12,15-17] and development of SLE at a young age has been shown to predict mortality in SLE.[18] Also, within the first year post diagnosis, 70% of children, as compared to only 28% of adults, develop features compatible with NPSLE.[19,20]

Specific differences in regard to neurological SLE symptoms between children and adults seem to include a significantly higher prevalence of focal deficits, such as pseudo tumor cerebri, transient ischemic attack, and seizures, as demonstrated by The Grupo Latino Americano de Estudio del Lupus (GLADEL) cohort.[21] The GLADEL cohort, however, incorporates children of multi-national Hispanic ethnicity, with socio-economic and genetic factors potentially specific to these communities, which may not be shared with different adolescent SLE cohorts from different sub-populations. For example, a Belgian study by Hoffman *et al*., instead found only a significant difference in higher frequency of encephalopathy (and renal disease and hemolytic anemia) between adolescent and adult SLE patients.[22] Despite this, however, a consensus from a few other small studies is that even in the absence of co-morbid conditions, chorea and cerebrovascular disease are reported in up to 25% of children with NPSLE, which may be more common than in adult SLE.[21,22] Antiphospholipid antibodies have been associated with abnormalities in cognitive function in both childhood onset and adult SLE.[23-25] Cranial nerve abnormalities, however, are more frequently encountered in adult SLE than childhood onset SLE.[12]

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Table 1. Case definitions for neuropsychiatric syndromes in systemic lupus erythematosus (American College of Rheumatology 1999).

Peripheral	Central
Mononeuropathy (single/multiplex), myasthenia gravis, plexopathy, polyneuropathy	Acute confusional state, acute demyelinating polyradiculopathy, anxiety disorder, aseptic meningitis, autonomic disorder, cerebrovascular disease, cognitive dysfunction, demyelinating syndrome, headache, mood disorders, movement disorder (Chorea), myelopathy, neuropathy, cranial, psychosis, seizures and seizure disorders

As regards diffuse deficit, a shared feature is depression, which is the most common mood disorder and is equally common in children and adults.[22,26,27] Psychosis, however, appears more common in children than adults with NPSLE, affecting between 7.5-12%.[2,28-30] A recent study of 500 adult SLE patients followed for 30 years, in contrast, reported a 2% prevalence of psychosis.[31]

Key challenges in study designs to date are of variability in definitions of neurocognitive impairment (particularly pre-1999 NPSLE criteria),[6] lack of appropriate controls, lack of large multi-centre prospective longitudinal studies, limited allowances for language barriers or ethnic, socio-economic and environmental differences, poor control of medications used to treat SLE or neuro-psychiatric manifestations and variable disease duration.

Normal cognitive development in the developing child and adolescent

Childhood onset SLE peaks in early adolescence. Understanding normal cognitive development in relation to developing neuroanatomy of the adolescent brain is a necessary prerequisite to understanding the pathogenesis of cognitive impairment in patients with SLE in this age group. Recent studies have shown important dynamic and complex differences between the child, adolescent and adult brain, which may have great significance for the understanding into the pathogenesis of NPSLE in general and how it may differ with age of onset. A study by Blakemore and Choudhury in 2006, describes normal structure and synaptic evolution in the developing child and adolescent brain.[32] As neurons develop, a layer of myelin is formed around their axons, from supporting glial cells. The myelin acts to increase the speed of transmission of electrical impulses between neurons. Sensory and motor brain regions become fully myelinated in the first few years of life, but axons in the frontal cortex continue to be myelinated well into adolescence. Early in postnatal development, the synaptic density (number of synapses per unit volume of brain tissue) greatly exceeds adult levels. The peak of synaptogenesis (at approximately 2 years of age) is then followed by a period of synaptic elimination (synaptic pruning), which is thought to be experience-dependent and occurs over a period of years. Synaptic densities in the prefrontal cortex have a different time course however, with proliferation in childhood then plateau. A second wave of proliferation develops in puberty, and then synaptic pruning occurs throughout adolescence, with a net decrease in synaptic density post puberty. Synaptic pruning is thought to be essential for fine-tuning functional networks, for example sound categorization relevant to language development.

During adolescence, as demonstrated with studies incorporating Magnetic Resonance Imaging (MRI), there is a linear increase in white matter in the frontal and parietal cortex, particularly the right internal capsule, left arcuate fasciculus (which connects anterior speech regions and posterior language regions), and the corpus callosum. Myelin appears white in MRI scans and so this white matter increase is thought to correlate with myelination.

There is also a non-linear decrease in grey matter during adolescence in this same region-specific manner. It is thought that the decrease in grey matter represents the synaptic reorganization that occurs at the onset and post-pubertal period.

The peak volume of grey matter in the frontal and parietal lobe occurs at about 12 years for a male and 11 years for females. Larger longitudinal studies are required to discern gender differences more definitively in the regional cortical variability seen in MRI studies so far. It is of interest that this time of significant evolution of the child to adolescent brain seems to coincide with the peak incidence of onset of childhood onset SLE. This evolution might perhaps be relevant to a different disease process in childhood onset NPSLE and neurocognitive impairment compared to adults. It also highlights the potential impact of this disease on future function and life, in this vulnerable period of cognitive development. In particular, studies including functional neuroimaging and performance tasks suggest emotion recognition abilities (such as recognition of fear, disgust and anger), decision making and risk/reward behavior are significantly different in adolescents compared to that in children and adults.

A study by Bjork *et al.*,[33] suggesting differences in brain activation in mesolimbic circuitry during incentive-driven behavior between adolescents and adults has led to a proposal that adolescents are driven to seek more extreme incentives to compensate for low recruitment of motivational brain circuitry. There appears to be more reliance on the prefrontal cortex than parietal circuits in adolescent brains than in adults.

Significant neural development and hormonal changes in adolescence obviously influence social and emotional behavior in adolescents and are likely to influence social cognition, which includes self-awareness and theory of mind, which, like executive function, are also high level cognitive capacities linked to the pre-frontal cortex.

Further studies, into the development of executive function and social cognition from childhood into adolescence and into early adulthood are very much required and will be important for more complete understanding of NPSLE manifesting in patients of these ages. It may be possible that these may help to explain why non-compliance with therapy for SLE occurs at such high rates in adolescent onset SLE. No such studies have yet been performed in childhood onset SLE. One recent study of adults with SLE, with age range of 43.44±14.96 years, has suggested that a young age and cognitive impairment, are two key predictors of non-adherence to treatment in SLE.[34] Another study, by Koneru *et al.*, of non-adherence in adults of slightly younger age range (33.6±15 years), although not finding young age significant, found busy life style, lack of family or social support as key, together with poor comprehension of instructions and low educational level as significant risk factors.[35] If these few adult studies suggest that educational, cognitive and social status of SLE patients, significantly impacts on treatment adherence, it lends weight to the importance of studying NPSLE in childhood onset SLE in greater depth, where development of these skills and functions, during active childhood disease, could be potentially affected.

Domains of neurocognitive function in childhood onset systemic lupus erythematosus and tools for assessment

Most studies (in adults with SLE) show deficits in areas of attention, verbal memory and also in major domains of complex problem

solving, working memory and visuo-motor integration.[3,36] Most adult SLE patients have an evanescent course of cognitive dysfunction (over a 2-5 year period) with only a minority showing progressive decline.[37-41] Similar longitudinal studies to demonstrate such patterns in childhood-onset SLE have not been performed. As in adult SLE studies, several pediatric SLE studies describe cerebral and cerebellar atrophy on anatomical MRI imaging.[42,43] More specifically in adults with SLE, at least one small case study (where n=5), have demonstrated hippocampal atrophy using similar MRI imaging techniques, compared to age and sex matched controls. This contributes to a commonly held theory that the hippocampus is pathologically linked to cognitive impairment in SLE, which is linked to demonstrable deficits in short-term memory.

Neuropsychometric tests

Formal neurocognitive tests still remain the standard for diagnosis of cognitive dysfunction in SLE, as per the ACR ad hoc Committee on neuropsychiatric lupus nomenclature, as part of the ACR nomenclature and case definitions for neuropsychiatric lupus syndromes (1999).

As initially tests were adult-orientated, the *ad-hoc* working group of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) SLE subcommittee, subsequently produced a standardized core set of the assessment of cognitive function in children and adolescents aged 9-18 years old (Table 2).[44] As yet, these are not validated in childhood-onset SLE, but seem to provide information on several key domains of cognitive function including executive function and working memory.

Most commonly however, computer-administered neurocognitive assessments have been applied, aiming to address the limitations of the CARRA core set including time factors (hours) and high cost, short attention spans, fatigue and language differences. Thus there was application of the more frequently used computerized battery of neuropsychometric tests, the Automated Neuropsychological Assessment Metrics (ANAM) devised in 1997, which takes only 20-45 minutes to complete with different language options (although still limited to English and Spanish) and was validated in adults with SLE in studies since 2003 and used in children over the age of 13 years since 1999. It has been correlated strongly with traditional paper screening tasks such as the Trail Making Test, the Stroop Color Word Test, and the Digit Symbol Test.[45-47]

In 2004, a pediatric equivalent, Pediatric Automated Neuropsychological Assessment Metrics (Ped-ANAM) was devised and used in children with SLE aged over 10 years old.[48] The Ped-ANAM is shown in Table 3.

Useful information on pediatric SLE has been gained using such tests as was shown in a study by Brunner *et al.* in 2007, where 59% of the childhood-onset SLE patients assessed with standardized neuropsychometric tests had neurocognitive dysfunction. This cohort was also significantly more likely to perform poorly more specifically in measures of visuo-constructional processing and short term memory than those childhood-onset SLE patients without cognitive dysfunction.[3]

Further studies by Brunner *et al*., including one presented at the 2011 ACR Conference, have demonstrated the reproducibility and validity of Ped-ANAM, with recommendations for its use in clinical practice.[44,49] However, it still has not been formally compared to other standard battery tests and although potentially cheaper and more efficient than other battery tests, without the requirement of a trained psychologist to administer, it still remains only a research tool at present for most pediatric/adolescent rheumatology departments.[46,47,50,51]

Another issue is heterogeneity of classification criteria for neurocognitive impairment. Recently published, was a prospective, cross-sectional, case-control study of 41 childhood onset SLE subjects, by Williams *et al*.[52] They combined three existing neurocognitive impairment (NCI) classification criteria to assess the prevalence of NCI in childhood onset SLE. Their American cohort was predominantly female, adolescent, urban, Hispanic and all English-speaking. They compared subjects with age- and ethnicity- matched healthy controls. The results were categorized using firstly the Brunner *et al*.[3] Categorization method, of assessing 4 domains (memory, psychomotor speed, visual construction processing and attention/executive functioning) using 11 tests, then a method by Mikdashi *et al*.,[5] where NCI is dichotomized into impairment and cognitive decline (also with focal versus multifocal domain impairment). Finally they used the Muscal *et al*.[42] method, which tests the ACR recommended seven domains in total, expanded to include academic achievement as a separate domain, using 19 individual tests. Total testing time was between three to four hours.

Interestingly they found no significant difference in prevalence of NCI (ranging from

Table 2. Proposed childhood arthritis and rheumatology research alliance neuropsychological assessment core set for children and adolescents with SLE (CARRA).

Name of measure	Cognitive domain tested	Duration of test (min)
WASI II: subtest version (vocabulary and matrix reasoning)	General intelligence	30
WISC-IV: coding and symbol search	Psychomotor speed	10
WISC-IV: digit span and letter-number sequencing	Verbal working memory	20
Conner's continuous performance test (CPT)-II	Attention	15
Woodcock-Johnson-III Achievement subtests: letter-word identification, reading fluency, calculations and math fluency	Academic skills, mastery	30
WRAML-2: screening subtests (story memory, verbal learning, picture memory and design memory)	Verbal and visual memory/learning	30
Stroop color and word test	Attention, cognitive flexibility, response inhibition	5
Delis-Kaplan executive function system verbal and design fluency subtests	Speed/executive functioning	10
Grooved pegboard	Manual dexterity/speed	5

7.3-63.4%) between the controls and patients, using any of the categorization methods. NCI was also not associated with SLE disease duration, activity or characteristics, anti-phospholipid antibodies nor with depression. They did, however, report significantly lower quality of life estimates in patients in the cognitive impairment group using the Muscal *et al.* method. They reflected that NCI prevalence varied according to the categorization method employed, with over-simplification of observed deficits possible in some, and the importance of studying an appropriate control group.

Limitations still exist in terms of developmental variability, learning effects (which develop after repetitive testing), relative lack of controls, lack of multiethnic samples, inconsistency of test batteries, no multicentre studies and ongoing time and expense issues. Any future longitudinal studies in NPSLE in children and adolescents will require consideration of the above, including appropriate statistical models for test-retest situations, taking into account the evanescent nature of NPSLE related neurocognitive dysfunction.

Association of regional brain activity and domains of neurocognitive function

Functional MRI (fMRI) is an important neuroimaging modality, currently used primarily for research, which records brain activation patterns associated with specific cognitive tasks and has been used in several studies to date in childhood and adult onset SLE.

It acquires serial images whilst the subject alternates between performing active and control tasks (fMRI paradigms). Image intensity is weighted by the relative oxygen level of blood hemoglobin (blood-oxygenation level dependent).[53] Contrast between images obtained during active and control task periods of a paradigm reflect changes in regional brain activity.

In a key study by DiFrancesco *et al*.,[54] fMRI was combined with a (non-CARRA or PED-ANAM) battery of standardized neuropsychological tests, to demonstrate significant age-dependent activation differences in 10 patients with childhood-onset SLE compared to healthy age-matched controls, in the attention [using continuous performance task (CPT)], working memory (using N-back task) and language paradigms (using verbal generation task). A deficit in word fluency in childhood-onset SLE seemed to correlate with reduced activation in the Wernicke area and altered activation in the Broca areas involved in word-finding and language processing. More activation in the fusiform gyrus and visual associative cortex, areas associated with abnormal attention, were also demonstrated in the childhood-onset SLE group. The frontal cortex and hippocampus, which mediate working memory, were also activated in the childhood-onset SLE cohort. This region has previously been shown, using other modalities such as single photon emission computer tomography (SPECT) and positron emission tomography (PET), to be important for working memory.[36,55-60] The enhanced activation during tasks relating to working memory observed in these areas in childhood onset SLE versus age matched healthy control imply that greater effort is exerted by these patients to perform this task. Evidence supports the notion that increased effort of a task results in enhanced activation on fMRI.[61-63] Fitzgibbon *et al*.[64] also examined working memory, executive function and attention in adult SLE patients and also found greater frontoparietal activation in adult SLE patients than healthy controls, implying also that the same cognitive operations required more cortical activity in SLE patients.

These fMRI studies demonstrate diffuse changes in brain network distribution as a plausible outcome of damage to critical connections between neural network elements. This seems to correlate with the systemic nature of SLE with temporal and variable flare onset, severity and duration.

fMRI does however have limitations in the sensitivity and reliability subtle changes of blood flow. These features might be influenced by abnormalities in the endothelial vascular bed that are known to exist in SLE and limitations of connectivity analysis, cost and time. Such studies require that the patients follow specific instructions in relation to undertaking relatively complex cognitive tasks. Thus fMRI studies are not practical in patients with severe NPSLE manifestations and remain experimental.

Table 3. Pediatric automated neuropsychological assessment metrics (Ped-ANAM). Total duration: 30-40 minutes.

Name of measure	Cognitive domain tested	Description
Simple reaction time	Reaction time	Repeated at end of battery to assess both within-session reliability and the effect of fatigue
Procedural reaction time	Choice reaction time	Processing speed (choice reaction time/rule adherence)
Code substitution and code substitution delayed	Attention, concentration, learning	Delayed recall task for explicit recognition memory
Logical reasoning	Executive functioning	Reasoning and verbal syntax
Spatial processing	Spatial analysis	Spatial processing
Continuous performance test	Sustained attention and working memory	Continuously monitor numbers and identify if each number is the same/different from the preceding letter
Mathematical processing	Arithmetic, attention, processing speed	Decide whether the solution to a simple arith metic problem (e.g. 2+3=6) is correct or incorrect
Matching grids	Visuo-spatial discrimination	Determine if 2 designs are the same/different
Matching to sample	Short term memory, attention, visuo-spatial discrimination	Select which, of 2 designs match a target design presented 5 seconds earlier
Sternberg memory search	Sustained attention and working memory	Memorize a string of 6 letters and later determine whether individually presented letters were included in the original string

Pathogenesis of neurocognitive impairment in systemic lupus erythematosus

The precise pathogenesis of NPSLE and its consequence, NCI, is unknown and most likely multifactorial. The UK Juvenile-onset SLE (JSLE) Cohort is a prospective, national, multicentre study, with several aims including elucidating pathogenesis of JSLE, using serological and clinical data from an ever-expanding cohort of SLE patients up to the age of 18 years. This cohort and studies associated with it, have the potential to advance our understanding of JSLE in general and hopefully juvenile-onset NPSLE, which may differ from adult-onset pathogenesis, and thus might explain some of the differences we see in clinical frequency, time of onset and severity between those of juvenile versus adult onset.[9]

At present however, there is a predominance of adult NPSLE studies, which propose the role of autoantibodies, cytokines, chemokines, matrix metalloproteinases and neuropeptides in the development of inflammation, alteration of the blood-brain barrier (BBB), thrombosis, vasculopathy, demyelination and neuronal cell death. The role of genetic variations and propensity to NPSLE remain poorly understood and various neuroimaging techniques have also been employed to elucidate anatomical, metabolic and functional and neuroanatomical abnormalities in NPSLE. This is broadly summarized in Figure 1, where it must be noted that the majority of presented potential bio-markers and imaging remains experimental only.

It is not clear if one mechanism or multiple mechanisms are responsible for symptoms. Symptoms wax and wane and active NPSLE incorporates heterogeneity of symptoms, with diffuse central nervous system (CNS) symptoms appearing more commonly than focal. Thus is it perhaps unsurprising that multiple mechanisms have been proposed. There is no standardized serum, cerebrospinal fluid (CSF), nor imaging tests or techniques, for the diagnosis of NPSLE or neurocognitive impairment in SLE. At present, there are also no reliable predictors for development of NPSLE, illustrated by a recent study of 67 adolescent SLE patients, 24 of whom had NSPLE found no differences in the clinical and laboratory results between the time of SLE onset and NP onset, so they could not identify any factors that might predict the occurrence of NP symptoms during an NP flare.[65] Proposed potential serum and CSF biomarkers for NSPLE however, are presented below.

Autoantibodies

Pediatric and adult studies have shown associations of several auto-antibodies to neurocognitive impairment in SLE, albeit the majority in adult studies, with some variable reports of incidence and reliability.

Anti-neuronal and anti-ribosomal phosphoprotein (anti-ribosomal P) antibodies are known to be associated with NPSLE but numerous studies show inconclusive results.[41,66,67] Some studies had proposed that elevated levels of anti-ribosomal P antibodies were found in 8-35% of adult patients with active NPSLE, suffering from psychosis and depression.[68-71] A meta-analysis of 14 published trials however concluded that serum anti-ribosomal P measurements were not sensitive in diagnosing NPSLE and did not distinguish between NPSLE subsets.[72-76] The few pediatric NPSLE studies so far have only demonstrated a higher prevalence of these and anti-dsDNA and anti-Sm antibodies, in childhood than adult onset SLE without any clear causal or

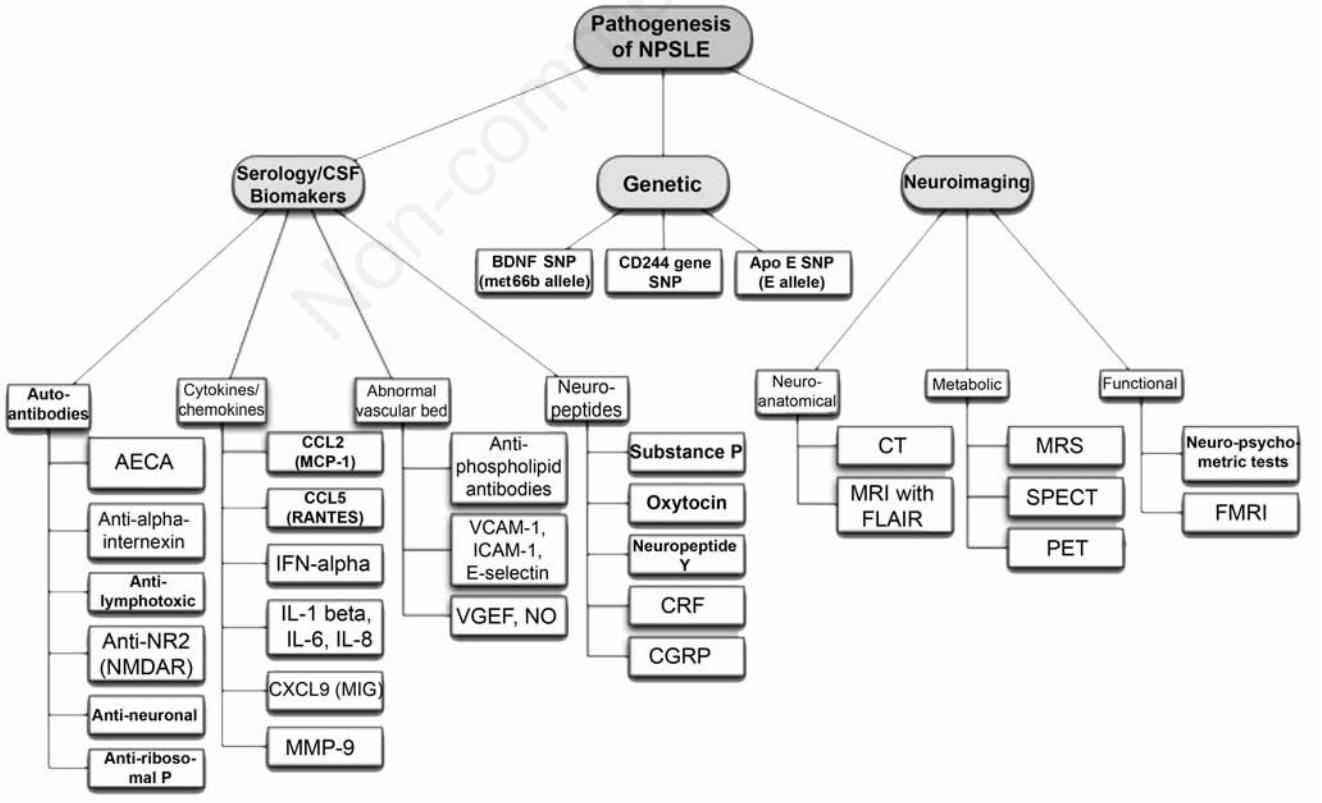

Figure 1. Pathogenesis of neuropsychiatric systemic lupus erythematosus.

pathogenic association yet elucidated.[4,77,78]

Our group at University College London (UCL), recently described the observation that serum anti-Sm antibodies levels correlate positively with higher levels of nitrated nucleosomes, a serum marker of nitrosative stress, as measured by a novel capture ELISA. From our small number of patients with SLE from the UCL Hospital Lupus Cohort, we also made an observation that nitrated nucleosome levels significantly correlated with SLE disease activity and also significantly correlated with NPSLE involvement as per validated BILAG and ACR classification evaluation.[79,80] As children most likely have a higher prevalence of serum anti-Sm antibodies than in adults,[14] it could suggest an aetio-pathogenic role of anti-Sm antibodies and/or nitrosative stress in the development of NPSLE, which could partially explain a higher incidence of NPSLE in children than adults. Further research into this and nitrosative stress in NSPLE is ongoing.

A consensus in published studies of both adult and juvenile-onset SLE, is that antiphospholipid antibodies tend to be associated with vasculopathy causing ischemic and other focal manifestations of NPSLE such as chorea, particularly in the few pediatric studies of these antibodies.[23,25,81]

There are only a few small studies suggesting a link in adults with SLE with lymphotoxic antibodies and cognitive impairment.[82] An antibody against a neurofilament, alpha-internexin, has been identified in one small Chinese study in 2010, in both the serum and CSF of approximately 50% of a small cohort (n=67) of adult NPSLE patients and was found to induce murine cognitive damage via inhibition of axonal elongation and promotion of cortical and hippocampal neuronal apoptosis.[83] Further studies are required however, to further investigate their role in NPSLE of both adult and childhood onset.

The few recent studies into significance of serum anti-ganglioside antibodies (AGA) in SLE in children and adults have interestingly shown discrepant results. A small pediatric study from Egypt in 2010 showed a significant positive association of AGA M1 antibodies with cognitive dysfunction and future risk of cognitive dysfunction, suggesting a predictive value.[84] However, a retrospective study this year of 65 adult SLE patients showed no correlation between several subtypes of AGA and neuropsychiatric manifestations of SLE.[85]

Anti-MAP-2 antibodies have been found in 76.5% of adult NPSLE patients and in SLE without NP disease, compared to controls with other neurological conditions. This is where MAP-2 is a cellular protein exclusively found in neurons, essential to cytoskeletal integrity so seems a plausible neurological antigen.[86,87]

Ongoing work into glutamate receptor biology may be relevant in elucidating insights into the underlying pathogenesis of NPSLE. It is known that a subset of anti-dsDNA antibodies cross react with the N-methyl-D-aspartate receptor (NMDAR).[88,89] NMDARs are receptors for glutamate, the major excitatory neurotransmitter in the brain, critically important for many brain functions such as conveyance of sensory information, response to motor commands and formation of thoughts and memories that translate to cognitive and emotional abilities.

NMDA receptors bind glutamate or glycine to their NR2 or NR1 subunit and allow calcium to flux into the cell. An excessive flux of calcium into neurons causes mitochondrial stress and activates caspase cascades leading to neuronal death.[90-92] Excessive exposure to glutamate is also implicated in several neurologic syndromes.[93] Receptors containing NR2A and NR2B subunits are most dense on neurons in the CA1 region of the hippocampus and amygdala, where it is known that hippocampal NMDARs are involved in learning and memory and amygdala NMDARs are critical in the fear conditioning response. This is of relevance for NPSLE given that studies demonstrating aberrations in hippocampal-dependent learning have been observed in experimental lupus with impaired murine capacity to navigate a visuo-spatial type of maze test after spontaneous development of lupus-like illness.[94-96] Of the few pediatric studies, Levy *et al.* in 2009, observed significant prevalence of anti-NMDAR antibodies in children with SLE, which did not predict neurocognitive impairment however, so the relevance of anti-NMDAR antibodies remains to be seen in NPSLE of any age of onset.[7]

More recently, reduced cerebral GABA (gamma-aminobutyric acid) receptor density in nine adult patients with CNS NPSLE correlating to memory loss and cognitive dysfunction, has been observed using SPECT neuroimaging, suggesting an alternative excitatory neurotransmitter receptor defect other than NMDA and Glutamine interaction, that may be relevant in the pathogenesis of NPSLE and requires further investigation in children and adults with SLE.[97]

The integrity of the BBB may be important in the pathogenesis of NPSLE. For example, it is known that serum anti-NMDAR (anti-NR2) antibodies access brain tissue only after a compromise of BBB integrity, that the same antibodies have differential effects on brain function depending on the region of brain exposed to the antibodies, and that insults to the BBB are regional rather than diffuse.[98] The presence of these antibodies in the CSF of patients with lupus also correlates with acute, diffuse CNS manifestations of NPSLE and with symptom severity.[99,100]

An *in vitro* BBB model created in 1996 by Hurst and Fritz using human ECV304 which express an endothelial phenotype, grown on rat C6 glioma cells, has been used in several studies to date to investigate endothelium, including characterization of anti-endothelial antibodies (AECAs).[101,102] AECAs, have been reported to be found in approximately 40% of SLE patients compared to multiple sclerosis, stroke and healthy controls in one study by Saadi and Platt.[103] The IgG from the SLE patients caused increased IL-6 release from IL-1β pre-treated endothelial cells, compared to control IgG. Another study demonstrated the ability of a monoclonal AECA isolated from an SLE patient to recognize a 42kDa endothelial cell membrane protein and activate endothelial cells, leading to up regulation of the gene-regulatory protein NF-κB, which is also implicated in a pro-inflammatory milieu.[104] Further work is necessary to see whether direct activation of the BBB may be another mechanism of CNS pathogenesis in NPSLE.

A key question remains whether pathogenic antibodies are produced peripherally or intrathecally within the CNS, by local resident B cells or whether both processes are important. Serum detection of several auto-antibodies consistently appears to have a weaker correlation of effect than CSF. For example, anti-NR2 antibodies show highest correlation with CSF *versus* serum detection.[100,105] Also, many SLE patients, including both children and adults, have circulating antiphospholipid antibodies without apparent manifestation of neuro-psychiatric disease. Anti-NR2 antibody may also be present in the CSF of lupus patients without clinically apparently CNS disease.

Studies into CSF analysis in SLE or NPSLE however are limited by ethical factors such as lumbar puncture being invasive and not without risk (particularly difficult to obtain consent in a pediatric population). The few case studies performed in adult diffuse NPSLE suggest that intrathecal antibody production is found in 25-66% of cases, with only six studies using patient groups with controls, in which 13-30% showed evidence of BBB damage and 80% detected intrathecal antibodies (also suggested by oligoclonal bands).[2,106,107] Limited antibody profile testing were performed, with the only significant finding that anti-cardiolipin antibody was not strongly associated with BBB damage, nor intrathecal antibody production.[108]

Cytokines and other proposed molecules

Cytokines, chemokines, matrix metalloproteinases and various neuropeptides have been implicated in NPSLE pathogenesis as shown in animal models of lupus.[109,110]

Overexpression of genes encoding the pro-inflammatory cytokines, interleukin-1β, interleukin-6 and interferon-γ, have been demonstrated in the hippocampi of MRL-lpr/lpr SLE mice. Atrophy and increased apoptosis in the

hippocampi of these mice has also been reported.[111,112] Raised intra-thecal Plasminogen activator inhibitor (PAI-1) levels in NPSLE correlate with increased CSF levels of pro-inflammatory cytokines and markers of neuronal damage.[113] The metalloproteinase, MMP-9, is known to play a key role in disruption of the BBB, with elevated levels seen in the serum and CSF.[114,115] Neuropeptides such as oxytocin, vasopressin, corticotropin-releasing factor, neuropeptide Y, substance P and calcitonin gene-related peptide have also been linked, with decreased levels of the latter three in the hippocampus found in a few studies in lupus-prone mice,[116] and elevated serum levels of neuropeptide Y levels in SLE patients, irrespective of steroid treatment, in another study.[117] The relevance of such mediators in the pathogenesis of childhood onset NPSLE specifically remains to be determined however.

More recently, higher intra-thecal levels of B-cell activating factor (BAFF) and B-cell proliferation-inducing ligand (APRIL) have been found in adult NPSLE patients (as defined by clinical features, severely impaired cognitive neuro-psychometric tests and abnormal MRI imaging), compared to those SLE patients without neuropsychiatric manifestations.[118] This is of particular interest as regards pathogenesis probably including auto-antibody production by B cells, hence this supports the use of the B cell blockade as the most recent therapeutic option for SLE in adults and children. This is of particular interest in childhood-onset SLE, given that the frequency of auto-antibodies is higher than in adults with SLE.

Disorder of the vascular bed

SLE is an independent risk factor for endothelial dysfunction,[119] which may be of relevance with regards to disruption of the BBB. Disorder of the vascular bed in NPSLE, has to date been mostly associated with studies into antiphospholipid antibodies with focal CNS pathology in adults. However, studies identifying markers of oxidative stress and endothelial activation, such as E-selectin, VCAM-1, ICAM-1, VEGF and nitric oxide derivatives, are also potentially important to further elucidate the role of a vasculopathy in the pathogenesis of NPSLE.

Neuroimaging

This may be broadly classified into imaging that delineates abnormalities relating to anatomical, metabolic or functional parameters, as summarized in Figure 1 (NB these imaging modalities remain mostly research tools at present).

Anatomical CT imaging has been of limited benefit in the diagnosis or characterization of NPSLE in either adults or children. It detects obvious structural pathology such as hemorrhage, thrombosis or mass lesions but nil else. Anatomical MRI, using spin-echo T2 weighted imaging and fluid-attenuated inversion recovery (FLAIR) and gadolinium contrast, is used more commonly in assessment for NPSLE in both adults and children but again provides limited sensitivity and limited information on cortical and sub-cortical neuropathology such as diffuse cerebral atrophy, non-specific increased T2-weighted signal foci in both grey and white matter and small cortical infarcts.[120-122] Muscal *et al.* found brain atrophy in cerebral (73.3%) and cerebellar areas (67.7%) in a small study of children with SLE without NPSLE symptoms, highlighting that the correlation of common brain volumetric abnormalities with clinical findings remains unclear.[42] It is of interest, however, that hippocampal atrophy is a consistent finding in both adult and children with SLE, supporting hippocampal involvement seen with adult fMRI and NMDAR receptor studies already mentioned.

Also intriguingly, an MRI study by Petri *et al*., further suggests the brain may be insulted early in disease course, perhaps prior to diagnosis of SLE, given that brain atrophy was also seen in 18% and focal lesions in 8% of SLE adult patients within 9 months of diagnosis.[123] Furthermore, a recent novel study using high-resolution structural MRI images and voxel-based morphometry (VBM) compared 20 adult acute NPSLE patients (up to 15 days after an acute event) with 18 SLE patients without NPSLE and 18 healthy controls. They showed increased grey matter atrophy in temporal and parietal regions, in particular the posterior thalamus bilaterally and also increased grey matter volume in the posterior para-hippocampal gyrus, in both NPSLE and SLE patients, without significant differences.[124] This further supports the idea that a subclinical neurodegenerative process occurs in SLE, requiring further research into whether specific neuropsychiatric symptoms are related to regional brain changes or not and whether this occurs at a different time-course, distribution or extent in childhood or adult onset SLE, given what we now know about differences in the normal developing child and adolescent brain compared to adults, and the increased frequency and severity of NPSLE manifestations in juvenile *versus* adult onset SLE.

Imaging techniques which measure metabolic activity in the brain such as Magnetic Resonance Spectrometry (MRS), PET and SPECT, although perhaps more sensitive in detecting more subtle changes, have also been limited in ability to provide association with clinical symptoms and tend to show at best only non-specific changes of hypometabolism, again mainly in adult SLE studies to date.

Increased choline:creatinine (Ch/Cr) ratio (particularly in the dorsolateral prefrontal cortex and white matter) using MRS has been found amongst patients with NPSLE compared to controls. This is where Ch/Cr is a marker of the glial and neuron transport system and is noted to be elevated also in other conditions involving inflammation, demyelination and gliosis, with relationship to executive function deficits such as in patients with Human Immunodeficiency Virus (HIV).[125-127] In adult SLE patients, moderate relationships with this ratio and complex attention, auditory attention and visual fluency have been noted.[125]

Several MRS studies have also utilized another neuronal marker investigated in NPSLE adult patients, N-acetyl aspartate, which is consistently shown as reduced in these patients. It correlates to cerebral atrophy, focal lesions, antiphospholipid antibody positivity and neurocognitive dysfunction.[128,129] Subsequently, it has been suggested from such studies that early myelin injury due to white matter inflammation precedes neuronal loss in SLE, which interestingly occurs in the absence of overt NPSLE manifestations.[128,130] A pediatric study looked at anatomic brain MRI and MRS in 24 children with SLE and 20 controls, which also found that 75% of their SLE patients had NPSLE clinical manifestations and 46% had abnormal MRI scans. Additionally, they noted that 4 of the SLE patients (16%) had significantly lower N-acetyl aspartate/Creatine (NAA/Cr) ratios than controls.[131]

Studies since the 1990's using SPECT in both children and adults still haven't shown a significant correlation between specific NPSLE manifestations and brain imaging abnormalities, just a high sensitivity of SPECT for detection of active CNS disease, but mainly in those with severe clinically evident disease anyway.[132,133] Additionally there is an interesting discrepancy of demonstrated focal hypoperfusion defects in context of diffuse or multifocal neurological manifestations, such as psychosis.[26,134] Again, such studies are limited by small sample sizes.

Fluorodeoxyglucose-PET (FDG-PET) has also demonstrated in adults only that 60-80% of active NPSLE patients have bilateral parieto-occipital white matter FDG-PET hypometabolism, even in the context of normal anatomical MRI scans.[135]

Diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI) allow assessment of white matter structure and integrity, with abnormal white matter in frontal tracts, corpus callosum and the thalamus detected in adult SLE patients, but these still remain research tools with limited clinical application in SLE patients.[120,136,137] For example, a 2011 study showed significantly different white matter correlates of neuropsychological dysfunction in NPSLE (left anterior thalamic radiation and right superior longitudinal fasciculus) compared to non-SLE (right external capsule), with no significant correlates in controls. However, there were no differences in terms of

depression between NPSLE or non-SLE groups.[138] Once again no such studies exist in childhood-onset SLE.

Magnetization Transfer Imaging (MTI) quantifies alterations in the properties of water protons in biologic tissue and other magnetic nuclei in macromolecule bound proteins in myelin, as they change physical state or chemical configuration. Selective damage to grey matter and abnormal cerebral activity in active adult NPSLE patients, using this technique has been seen, but again is limited in terms of showing association with clinical symptoms of cognitive deficit. Such studies are required for childhood and adolescent onset SLE.

Manganese-enhanced MRI (MEMRI) has been used in one Israeli study in mice with experimental NPSLE induced by anti-ribosomal-P antibodies (injected intra-cerebra-ventricular), using intra-nasal injection of manganese for this imaging technique. This enabled in vivo mapping of functional neuronal connections in the brain, including the olfactory tract. Significant reduction of MRI T1 signal enhancement in the olfactory tract, thought secondary to damage (including edema such as may be seen in lupus cerebritis), was associated with depression-like behavior and diminished sense of smell.[139] This was significant when compared to a control group injected with healthy human IgG antibodies. Also, reduced MRI intensities, without manganese injection, although not significant for each region, were demonstrated in the experimental NPSLE group when compared to the control group. This study supports the observation of olfactory/limbic system involvement suggested by those MRI studies in adult SLE patients with hippocampal and amygdala atrophy.[140,141] Again, this invasively enhanced imaging technique has been limited, however, to animal work.

Imaging evaluation of vasculopathy is difficult, with CT and magnetic resonance angiography used in clinical practice but of limited ability to detect small vessel pathology and they are not specific for NPSLE. Invasive arteriography is also not practical and is difficult in terms of consent in a neuro-cognitively impaired individual, especially a child or adolescent.

Functional imaging, correlating neurocognitive domains to areas of increased or decreased activation on fMRI studies and other functional imaging techniques have been summarized in the section on Domains of neurocognitive function in childhood onset SLE.

Genetics

The role of genetics in the pathogenesis of NPSLE is not well explored.

Brain-derived neurotrophic factor (BDNF), abundantly expressed particularly in the hippocampus, is associated with activity dependent synaptic plasticity, learning and memory processing. The Met66b allele, a functional single nucleotide polymorphism of the BDNF gene, has been associated with better cognitive functioning in the psychomotor and motor domains, proposed to confer protection against cognitive decline in patients with chronic SLE.[142-145]

Apolipoprotein E polymorphism is thought to be associated with NPSLE. Apolipoprotein E is thought to have an immuno-modulatory effect on T cell function and repair mechanisms of neuronal damage. A small study found a significantly higher frequency of the ε4 allele in adult patients with peripheral NPSLE than with central NPSLE, but there is no significant association with disease course or severity of NPSLE.[146]

Single nucleotide polymorphisms of the CD244 gene are also thought to predispose to renal and neuropsychiatric manifestations of SLE. A study of 243 adult SLE and 369 healthy controls were enrolled, with a strong association of the rs6682654 C and rs3766379 T alleles found with nephritis and neuropsychiatric lupus.[147]

Further studies, including comparison to non-SLE controls in the context of cognitive performance tasks, however are required to investigate these and other genetic markers in the future, to elucidate the significance of genetics in development of NPSLE. What is apparent however is a lack of genetic studies in children and adolescents with SLE.

Treatment of neuropsychiatric childhood-onset systemic lupus erythematosus

As for clinical pathogenesis and diagnosis, there is little evidence-base for treatment options for NPSLE in adults, let alone patients with childhood onset. Therapies remain largely anecdotal and non-validated. Compounding this management issue, is the anecdotal observation that even after treatment, symptoms of NPSLE can take up to 6 months to acquiesce. Additionally the side effects of current pharmacological therapies are significant and not fully understood.

Pharmacological therapies

Immunosuppression is proposed if there is evidence of CNS vasculitis or inflammation, but only after the exclusion of infection and non-SLE causes, which usually delays treatment, as it can be difficult to differentiate between these.

Glucocorticoids are the most commonly used treatment in both adults and children. However, only one double-blind, placebo-controlled study exists, conducted in 1994, studying glucocorticoids in SLE-associated cognitive dysfunction, with limited data on an apparent improved cognition in five of eight patients post a trial of daily prednisolone dose of 0.5 mg/kg, but of unknown duration of benefit.[148] The potential side effect of steroid-induced psychosis is also a complicating factor, with limited understanding of its effect on the BBB and difficulty in clinically differentiating it from SLE-induced psychosis, which is more common in childhood- than adult-onset NPSLE. Long-term side effects of glucocorticoids are numerous and notorious, with weight gain, acne, growth retardation and reduced bone density being of particular concern to the child or adolescent patient and their parents.

Cyclophosphamide, an intravenous or oral alkylating cytotoxic agent, is often used for severe manifestations of NPSLE (*e.g.* cerebrovascular vasculitis and transverse myelitis) in both adults and children. Again, however, potential side effects of infertility,[149] nausea, alopecia, mucosal ulceration and extravasation can complicate it's use and make the younger patient and their parents hesitant to use it, again with risk of delay of therapy. Subsequent use of disease modifying agents for maintenance therapy, including Hydroxychloroquine, Mycophenolate Mofetil and Azathioprine are often used but without clinical trial evidence base for efficacy in NSPLE.

The role of B cell depletion in NPSLE is unclear, although theoretically beneficial, where NPSLE pathogenesis probably includes auto-antibodies and where Rituximab (chimeric, anti-CD20 monoclonal antibody) treatment anecdotally appears successful for various organ manifestations of SLE in adults and children.[150,151] Belimumab, a human monoclonal antibody targeting B lymphocyte stimulator now approved for use in adults with SLE, also requires further evaluation to suggest particular benefit for NPSLE and use in children. Hence further randomized control trials, with additional inclusion of NPSLE and childhood-onset patients are required. Understanding the similarities and differences of B cell biology between childhood- and adult-onset SLE would also aid extrapolation of clinical trial results from adult to childhood onset SLE.[152]

Intravenous Immunoglobulin (IVIG) and plasmapheresis have been used in adults with refractory NPSLE, given their efficacy in other severe refractory manifestations of SLE such as renal, hematological disease and pregnancy loss associated with anti-phospholipid antibodies. These are expensive and invasive therapies, however, requiring specialist tertiary level care or resources not readily available in most centers and again are without evidence base in NSPLE for any age of onset and could be more traumatic for younger patients and

their families.

As regards cognitive impairment, there has been one randomized, placebo-controlled trial for a non-competitive N-methyl-D-aspartate receptor antagonist, Memantidine (currently used in Alzheimer's disease), in adult SLE patients. There was no significant cognitive improvement at 12 weeks, but this study was limited by inclusion criteria which didn't include the presence of anti-NR2 antibodies and no comparison with children/adolescents with SLE.[153]

Anti-platelet and anti-coagulation therapy is still controversial, with regard to theoretical vascular and thrombotic pathogenesis in the absence of anti-phospholipid antibodies, with only one longitudinal observational study showing that regular aspirin use in adult SLE was not associated with better cognitive performance compared to those who were not.[154] Again no such study exists in childhood-onset SLE.

Anti-psychotics and anti-depressants use, common for NSPLE patients of any age but without clinical trial evidence-base, often are complicated by common side effects including drowsiness and weight gain and hence lead to non-adherence issues. Additionally, their own effects on neuro-cognition are poorly understood and can complicate evaluation of NPSLE disease activity and prognosis.

Non-pharmacological therapies

Cognitive rehabilitation, such as psycho-educational group intervention, used in other non-SLE neurocognitive conditions may be useful, as suggested in studies of adults with SLE, by Harrison *et al*.[155] and Haupt *et al.*[156] This has not yet been fully explored in childhood onset SLE. It may not be of a similar benefit for those of a younger age of onset however, given likely differences in decision-making, social cognition and shorter attention spans than adults.

Multi-disciplinary team management is likely important however, to ensure all aspects of care are optimal, reduce non-adherence to medications and follow up and to support patients and their families through difficult NSPLE-related issues in the immediate to long term.

Conclusions

NPSLE comprises a heterogeneous group of disorders, which affects patients with SLE of all ages. However, comparative studies reveal that NPSLE probably does occur in childhood onset SLE with increasing frequency and severity compared to adults. Such comparative studies remain hampered by the absence of a validated core set of NPSLE manifestations in childhood onset SLE. The majority of clinical, basic science and imaging studies have been conducted in adult-onset SLE. Extrapolation of these findings to NPSLE in children and adolescents may not be appropriate, given the dynamic development of the adolescent brain and how this impacts on neurocognition in children, teenagers and young adults.

Pathogenesis of NPSLE in general has been linked to various autoantibodies, cytokines and neurometabolites. The question as to whether auto-antibodies access the CNS through a disruption in the BBB or are secreted in the CNS de novo remains to be elucidated. The genetics of childhood onset NPSLE also remain to be explored. Neuroimaging is helpful in identifying focal, structural abnormalities and fMRI studies may hold some hope in helping to delineate paradigms of neurocognition that are abnormal and map these abnormalities to the relevant neuroanatomical landmarks. Longitudinal fMRI studies in the developing adolescent brain and also comparative fMRI studies of adolescents and adults with SLE could help to identify and comprehend the differences observed between children and adult onset NPSLE. Limited availability of specific treatment options, during this important developmental stage, compounded also by incomplete understanding of predictors for poor adherence to treatment, makes the case for further scientific study of NPSLE in children and adolescents with SLE all the more compelling.

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