

Adding to complexity: Co-morbidity in paediatric rheumatic disease

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Abstract

Novel therapies including biologic agents offer paediatric rheumatologists significant opportunity to improve long-term prognosis for children with rheumatic disease. However co-morbidities related to the diseases themselves and their treatments, pose specific challenges to be overcome. Prompt recognition and appropriate management will improve quality of life, effectiveness of treatment, and overall prognosis. In this review we discuss key areas of co-morbidity frequently encountered in paediatric rheumatology including cardiovascular, renal, genitourinary and visual co-morbidity, bone health, drug related issues and the influence of rheumatic disease on growth and puberty.

Introduction

The care of children and young people with severe, often rare, multi-system autoimmune rheumatic diseases poses a significant challenge to multi-disciplinary specialist teams (MDST) endeavoring to provide holistic care to patients and their families. This is compounded by a striking paucity of a rigorous evidence base for their management [1]. Childhood and adolescence is a time of profound biological development and psychological change – all of which confer additional impact on chronic, complex inflammatory conditions. Many drugs used to treat these disorders have major potential short-, medium- and long-term side effects that many young people and their parents find intolerable [2]. Compounding the complexity in managing paediatric rheumatic disorders, are the frequent occurrence of single or multiple comorbidities. These can impact significantly on the disease process itself, treatment choices, and contribute to the full impact of the problems to be

faced by patients and their families.

Comorbid conditions may be directly linked to the underlying disease process itself and / or treatments, or may occur independently. Increased recognition and efforts to appropriately manage comorbidities is driven by greater expectation of outcome, the significant potential impact that they can have on quality of life, and the improved prognosis of the primary disease. Diverse comorbid conditions influence outcomes differently; pulmonary and cardiac comorbidities may increase mortality; whereas localised growth abnormalities such as micrognathia may associate with low mood and depression. As many outcome studies in paediatric rheumatology predate the current approaches to treatment it is not easy to extrapolate the relevance of these data to patients presenting currently [3,4]. Such studies can also be difficult to compare due to differences in the terminology used internationally (e.g. juvenile idiopathic arthritis (JIA), juvenile rheumatoid arthritis (JRA), juvenile chronic arthritis (JCA)). Notwithstanding these challenges, we discuss key areas of co-morbidity frequently encountered in paediatric rheumatology, including cardiovascular, renal and visual co-morbidity, bone health, and the influence of rheumatic disorders and treatment on growth and puberty.

Cardiovascular co-morbidity in paediatric rheumatic disease

Atherosclerosis is a chronic inflammatory condition itself influenced by rheumatic disease-related factors such as immune complex formation, complement activation, anti-phospholipid antibodies, inflammation, corticosteroid use and endothelial dysfunction [5-8]. Significantly increased mortality from cardiovascular disease reported in adults with rheumatic

disease is likely to be due in part to a clinically silent atherosclerotic process beginning during childhood. In JIA, atherosclerotic lesions have been demonstrated in post mortem specimens of children [9].

Carotid intima-media thickness (CIMT) has been validated against pathological studies to assess pre-clinical atherosclerotic plaques in adults [10]. CIMT is increased in children with systemic-onset JIA, juvenile-onset systemic lupus erythematosus (JSLE) and adults with a history of juvenile dermatomyositis (JDM), compared to controls [6,7,11,12]. Phase contrast magnetic resonance imaging (MRI) demonstrates aortic compliance and distensibility is reduced in JIA, indicating endothelial dysfunction and subclinical atherosclerosis [6]. Doppler ultrasound of the brachial artery measuring flow-mediated dilatation (FMD) is impaired in children with JIA and adults with JDM as compared to controls [5,12]. Novel methods of screening premature atherosclerosis in young people such as static / dynamic nail fold video-capillaroscopy have been proposed [9].

The prevalence of traditional cardiovascular risk factors (hypertension, body mass index, hyperlipidemia, impaired glucose tolerance, reduced aerobic fitness), are observed in children with rheumatic diseases [13-5]. Studies of lipid metabolism in children with JSLE demonstrate that dyslipoproteinaemia appears inherent to the disease process with depressed HDL, and elevated VLDL cholesterol and triglycerides [11]. Lipid abnormalities occur early in the JSLE disease course (within the first 4 years) [13]. Treatment with corticosteroids exacerbates dyslipoproteinaemia, increasing total cholesterol,

VLDL-cholesterol and triglycerides [14]. In adults with SLE, hyperhomocysteinemia is implicated in the pathogenesis of coronary artery disease and linked to thromboembolic events. Studies in JSLE have reported raised homocysteine levels although further prospective, long-term studies are required to further elucidate its role as a cardiovascular risk factor in children [16,17].

Studies of atherosclerosis prevention in paediatric rheumatic disease are lacking. As children and young people with rheumatic disease increasingly have less physical and functional disability, MDST's should provide advice and encouragement to facilitate lifestyle changes, which reduce obesity and improve fitness. Use of hydroxychloroquine has been associated with reductions in cholesterol and apolipoprotein B levels in JSLE, and lower cholesterol, low-density lipoprotein levels and vascular event frequency in adult SLE [18-20]. Statin use is reported as being associated with a variety of inflammatory myopathies, and is consequently usually avoided in such conditions [21].

In JSLE, the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) trial [22] randomised patients to either atorvastatin or placebo and assessed whether 3 years of treatment was effective in reducing atherosclerosis progression as measured by CIMT. Atorvastatin did not have a statistically significant effect on mean CIMT progression; however, CIMT progression rates were significantly higher in the placebo group than those previously reported for the general pediatric population and children with familial hypercholesterolemia. This supports the view that JSLE patients are

at increased risk of atherosclerosis. Cholesterol and LDL levels also decreased significantly from baseline in the treatment group. Importantly, the adverse events rate was comparable between treatment and placebo groups over the 3-year treatment period [22]. This trial, the first RCT of its kind in paediatric rheumatic disorders, exemplifies some significant challenges inherent to paediatric research that compounds the challenges of addressing additional issues related to co-morbidities such as cardiovascular risk (see Table 1).

Renal and genitourinary co-morbidity in paediatric rheumatic disease

Co-morbidity due to renal disease is more prevalent and generally more severe in JSLE as compared to adult-onset lupus, with up to 80% of JSLE patients having renal disease at some point in their disease course [24]. There is significant concern that irreversible renal damage may occur prior to the onset of clinically detectable disease [25,26]. Up to 20% of children with proliferative lupus nephritis (LN) develop renal failure over a 10-year period [27]. Potential biomarkers of early LN disease, disease flares and predictors of disease remission are increasingly being studied and a number have been identified [28] and include: urinary monocyte chemoattractant protein-1 (MCP1), Alpha-1-acid glycoprotein (AGP) [29], serum CXC motif ligand 13 (CXCL 13) [30], B-cell activating factor (BAFF), regulated upon activation normal T-cell expressed, and secreted (RANTES), soluble vascular adhesion molecule 1 (sVCAM-1) and complement fragments Bb, C3d-C1c and C5. Complement fragment C1q is reduced in LN [31]. The optimal biomarker or combination of parameters requires further longitudinal analysis to determine

which are best at predicting LN flares.

Historically renal amyloidosis was a major complication of JIA and other paediatric connective tissue disorders, now significantly reduced through use of intensive immunosuppressive treatment regimens [26]. ANCA-associated glomerulonephritis can occur, albeit rarely in systemic-onset JIA and focal segmental glomerulonephritis / mild mesangial glomerulonephritis have been reported in children with polyarticular JIA [32,33].

Bone health in paediatric rheumatic disease

Decreased bone mineral composition (BMC) and density (BMD) along with increased fracture risk can occur in children with rheumatic diseases, resulting in considerable pain and co-morbidity [34-9]. Peak bone mass is reached at the end of adolescence and is an important determinant of osteoporosis and future fracture risk. Multiple factors may contribute to osteopenia, including inflammation, corticosteroid use, diseases activity, nutrition, physical inactivity, limited exposure to sunlight and delays in pubertal development, all potentially important in a young person with a rheumatic disorder [34,35,39-43]. Even in the absence of corticosteroid treatment, 30% of post-pubertal female patients with mild-to-moderate JIA have low total body BMC [39]. Similarly, young adults with JIA can have abnormal BMD, despite achieving full disease remission [44,45]. Further studies which explore potential factors contributing to low BMC / BMD are highlighted in Table 2.

Studies investigating biochemical markers of bone turnover in JIA demonstrate increased bone reabsorption over bone formation, although some studies show a reduction in bone formation only [36,39,46].

Abnormalities in bone turnover are associated with increased disease activity, joint destruction, longer disease duration and pro-inflammatory cytokines [47,48]. Anti-tumor necrosis factor (TNF) treatment in methotrexate (MTX)-refractory polyarticular JIA patients is associated with significant improvements in lumbar spine BMD Z score and bone mineral content [49].

A negative correlation between bone mass and cumulative glucocorticoid dose occurs in children with variety of underlying diseases treated with glucocorticoids [50]. During childhood and adolescence, glucocorticoid treatment impairs bone mass accumulation, leading to a lower peak bone mass. High dose MTX in cancer treatment is associated with osteopenia but does not negatively influence bone mass at the doses used in paediatric rheumatic diseases [50].

Bisphosphonates are an effective treatment for osteoporosis in adults, with studies showing improvements in BMD and a reduction in fracture risk. Much less is known about their use in children. A recent review looking at the effectiveness of bisphosphonates in JIA patients with fragility fractures, found treatment to increase mean spinal BMD by 4.5-19.1% [52]. Further studies are required to clarify whether these positive effects continue over time, the length of treatment required, the maximal bone mass that can occur and the long-term effect on fracture risk [52]. Calcium, vitamin D and calcitonin have also been looked at in small studies but similarly these studies do not address longer-term outcomes [36].

Physical activity is a major non-pharmacological method for increasing and maintaining peak BMD and strength. Adults who participate in high impact

sports and exercises have a higher BMD [53]. Studies in healthy children have supported the efficacy of weight bearing exercises in increasing BMD [54]. Studies addressing the amount, duration and frequency of weight bearing exercise, along with safety and efficacy of such exercise regimens in paediatric rheumatic disease are necessary. Alcohol intake and smoking are associated with osteoporosis and increased fracture risk and should be discussed with adolescent patients [55].

Ophthalmological complications of paediatric rheumatic disease

Uveitis occurs in 12-38% of JIA patients [56-8], often asymptotically. The presence of uveitis may precede the development of arthritis, and often flares of uveitis and arthritis do not co-occur [59] emphasising the need for eye screening [60]. Severe JIA-associated uveitis is associated with cataracts, increased intra-ocular pressure, band keratopathy and posterior synechiae in up to 75% of cases [59,61,62]. The risk of developing uveitis varies according to the subtype of JIA with patients with oligoarticular disease having the highest frequency of uveitis, followed by polyarticular and systemic onset subtypes [59,61]. Other risk factors include: female gender, <6 years old at diagnosis and having JIA for <4 years [63]. Uveitis-associated complications are more likely in those who develop chronic uveitis, psoriatic JIA, a diagnosis of uveitis prior to, or at the time of arthritis onset, or in patients who are symptomatic at the time of uveitis onset [64]. Visual outcomes and rates of complications in JIA-associated uveitis are summarised in Table 3.

Topical corticosteroids are first-line treatment of JIA-associated uveitis

although complications include: increased intraocular pressure and cataract formation. Systemic corticosteroids and peri-ocular steroid injections may be required in refractory cases. Increasingly systemic immunosuppressive agents are used to reduce the risks of sight threatening complications and achieve a steroid sparing effect. MTX is well established as the first line disease-modifying agent in JIA; however, 15-50% of children will have refractory uveitis despite optimal treatment with MTX [67]. Anti-TNF agents vary in their efficacy in severe refractory uveitis [68], and reports of new-onset uveitis-associated with etanercept use in JIA [69] has lead to the preferential use of infliximab or adalimumab in JIA patients with uveitis. When treatment with one sub-type of anti-TNF has been ineffective switching to another anti-TNF agent can be successful in achieving control of intra-ocular inflammation [67].

Growth in paediatric rheumatic disease

Growth disorders are common in children with chronic rheumatic diseases and have been attributed to a range of contributing factors including disease duration and severity, age at diseases onset, immobility, sub-optimal nutrition and corticosteroid therapy. In JIA, the prevalence of significant short stature (final height z-score defined as less than twice the standard deviation score adjusted for age) ranges from 11% of all JIA, to 41% of patients with systemic-onset disease [3,70,71]. JSLE patients show a significant reduction in parent-adjusted height z-scores, with males being most affected [72]. The children most at risk of having a height deficit were those that presented in the pre-pubertal / peri-pubertal period, who were treated with >400mg/kg

cumulative dose of corticosteroids. Further follow-up studies exploring the effects of biologics, steroid-sparing regimens and improved disease control on growth are warranted.

Growth hormone (GH) and insulin like growth factor (IGF-1) are the most important regulators of growth out with the neonatal period. In children with JIA and significant growth impairment, low levels of IGF-1 are described with normal on-going pulsatile GH secretion [36,73]. Table 4 describes the relationship between the inflammatory cytokines implicated in rheumatic disease and hormonal regulators of growth. JIA patients treated with GH for one year can achieve a significant increase in height velocity [75]. In children with systemic and polyarticular JIA, GH therapy improves height velocity but not necessarily the predicted target height (final height z-score -1.6 in treated patients and -3.4 in controls) [76]. GH therapy for children with severe JIA receiving 12-15 months of steroid treatment can normalise height velocity during the first year of treatment, remaining normal over the subsequent two years [77]. Collectively these studies suggest that GH improves short-term height velocity but may not entirely reverse the effects of treatment and underlying disease on growth.

The pattern of growth disturbance in JIA can be generalised or localised and tends to vary according to the subtype. More severe JIA is associated with generalised growth impairment. Oligoarticular JIA typically can be associated with increased growth in the affected limb in young children and decrease growth due to premature fusion of the epiphyses in older children [73-4] resulting in limb or digit length discrepancy, or micrognathia. In practice,

growth retardation, especially localised is felt to be becoming less common with current treatment approaches, and often is a feature of delay in access to specialist care. Growth can be reversibly impaired during periods of intensive steroid therapy [78] although full catch-up growth is not always attained following cessation of steroid treatment [79].

The impact of anti-TNF treatment on growth velocity has been studied in polyarticular JIA patients. Those with delayed growth before anti-TNF treatment displayed a significant increase in growth velocity at two years after commencing treatment [80]. When glucocorticoid dosage was corrected for, the change in inflammatory activity emerged as a significant predictor of growth velocity, suggesting that reduced inflammation affected growth velocity rather than the anti-TNF treatment having a direct effect on growth. Comparing growth velocity in new polyarticular JIA patients treated with MTX alone and patients who had etanercept added to MTX treatment due to inadequate disease control, indicates growth velocity only increases significantly in the group receiving etanercept [49]. Similarly, looking at polyarticular and systemic-onset JIA patients treated with etanercept, etanercept and MTX or MTX alone for three years, statistically significant increases in mean height were only seen in those who received etanercept, with or without MTX [81].

Puberty in paediatric rheumatic disease

Pubertal delay has been reported widely in adolescents with paediatric onset rheumatic diseases. In JSLE, pubertal onset may be delayed in as many as

15% and 24% of the female and male JSLE patients respectively [73]. In a Brazilian study involving 30 patients with JSLE and 30 matched controls, mean menarchal age was 13.1 years in lupus patients versus 11.6 years in controls [82]. A high prevalence of menstrual disturbance is reported in JSLE, varying from irregular menses, long cycle lengths to postmenarche amenorrhea [72,82]. The hormone profiles of adolescent females with JSLE differ from healthy controls, with increased median follicle stimulating hormone levels and lower median progesterone levels [82]. In JIA, age of onset of menarche has been compared between patients and their mothers, revealing the timing of menarche to also be later in JIA and particularly delayed in patients who had systemic / polyarticular JIA or received glucocorticoids [83].

Quality of life

Chronic illnesses can lead to significant physical and psychosocial comorbidity. Paediatric rheumatologists have increasingly become aware of the need to measure health-related quality of life (HRQOL). A number of assessments can be used to do this, including the Child Health Questionnaire (CHQ) and Pediatric Quality of Life Inventory (PedsQL) [84,85]. Three international studies have assessed HRQOL and its determinants in JIA, JSLE and JDM [77,86,87]. In all three studies, significant impairment of HRQOL was identified in the physical domains of the CHQ. Physical well-being was correlated with the degree of functional impairment [86-8], whereas pain had the greatest influence on psychosocial health [86]. Patients with persistent oligoarthritis had better HRQOL compared with other subtypes of

JIA, whereas patients with systemic arthritis, polyarthritis, and extended oligoarthritis had similar HRQOL [86]. In JSLE, the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score was significantly correlated with the physical and psychosocial summary scores of the CHQ. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) score was also significantly correlated with the physical summary score, suggesting that HRQOL in JSLE may be affected by disease activity and accumulated damage [87]. In JDM, poorer physical and psychosocial summary scores were associated with increasing levels of disease activity and reduced muscle strength [88].

QOL assessment in adults with all types of JIA indicates a profound effect on generic health status and QOL at a median age of 30 years. Despite excellent educational attainment, a high rate of unemployment amongst these patients can exist [89,90]. The challenge with modern therapies and transitional care programmes is to improve outcomes relevant to patient priorities – being employed has considerable impact on well being and QOL but the impact in adult cohorts may not be fully evident until years to come, when these patients reach their third and fourth decade.

Drug related co-morbidity

Many medications used in paediatric rheumatology can have potential side effects. Non-steroidal anti-inflammatory drugs (NSAIDs) are associated with acute kidney injury, hypertension and interstitial nephritis in children. A prospective study evaluating renal complications in JIA patients treated for ≥ 6 months with NSAIDs found 22/226 children (10%) had microscopic

haematuria and/or proteinuria on ≥ 1 urinalysis. No patients developed hypertension and in 21/22 patients the abnormalities resolved spontaneously [91].

MTX is one of the most useful and commonly used drugs in paediatric rheumatology due to its efficacy and the availability of long-term safety data. Intolerance to MTX, namely nausea and vomiting, stomach ache, sore mouth and behavioral symptoms may occur in up to 44% of JIA patients receiving oral MTX and 67% receiving parenteral treatment [92]. Symptoms can occur after taking MTX, prior to (anticipatory), and when thinking of MTX (associative). Newer biologic treatments have transformed the management of JIA patients with MTX intolerance and MTX-resistant disease. However, with an increasing number of clinical trials and the consistent availability of these agents only within recent years, longer-term safety data are not available, and their long-term use as first line agents remain cautionary.

In 2009, the Food and Drugs Association (FDA) issued a warning related to the potential development of malignancies in patients with JIA who had used anti-TNF medications for more than 2.5 years. This was based on a study that included 48 children with both JIA and inflammatory bowel disease who developed cancer whilst receiving anti-TNF therapy and other immunosuppressive agents. These findings clearly cannot be ignored, but recent data suggest that JIA per se and not the exposure to MTX or biologics may associate with an increase risk of malignancy [93]. In rheumatoid arthritis (RA), evidence has accumulated that disease activity itself is associated with risk of lymphoma [94]. Observational studies exploring

the link between anti-TNF treatment and cancer risk have not indicated any increased risk of cancer, although the follow-up periods have been rather short (mean follow-up of 3 years) [95]. More investigation in this matter is therefore warranted. Biologics Registries in the UK and elsewhere have been collecting information on long-term safety and effectiveness of biological agents in patients with rheumatic diseases since 2000. Longer-term follow-up and collaborative collation of data internationally is necessary to improve reliability of these observations and fully address the concerns regarding paediatric rheumatic disease, biologic treatment and malignancy.

Cyclophosphamide is used to treat severe manifestations of JSLE, JDM and vasculitis. Bladder toxicity, cancer and haemorrhagic cystitis are seen in oncology patients where prolonged courses of oral cyclophosphamide are used. In autoimmune rheumatic diseases where intermittent intravenous cyclophosphamide is used such complications are rarely seen. Lowering the cumulative dose, concomitant use of MESNA, intravenous therapy and adequate hydration are all important in minimising risks [96]. Increased risk of cervical dysplasia is associated with cyclophosphamide use in SLE. It is important that young women with lupus follow established guidelines for cervical cancer screening and human papilloma virus vaccination [97,98].

Mortality associated with paediatric rheumatic disease

Studies looking at mortality in paediatric rheumatic disease are largely unable to determine the influence of co-morbid disease on mortality due to the lack of adequate longitudinal follow-up. Adults with a history of JIA and a co-morbid autoimmune disease (e.g. autoimmune hepatitis, insulin dependent diabetes

mellitus, common variable immunodeficiency, graves disease) have a shorter life expectancy than age and sex-matched members of the general population [99]. Data from the Indianapolis paediatric rheumatology registry [100] has been used to describe the standardized mortality ratio (SMR, ratio of observed deaths to expected deaths) and causes of death of a cohort of paediatric rheumatology patients (49,023 patients studied between 1993 and 2001). The SMR was increased in patients with JSLE and JDM (3.06 [95% CI 1.78–4.90] and 2.64 [95% CI 0.86–6.17] respectively). For patients with all types of JRA, SMR was less than that of the cohort as a whole. Causes of death were related to the underlying rheumatic disease and its complications in 35%, and treatment complications in a further 10% of patients.

Transition

Transition from paediatric to adolescent to adult rheumatology services is a particularly challenging time when young people are expected to take increasing responsibility for their own health and well-being; however the difficulties many young people face is exemplified by reduced adherence to treatment regimes, risk taking behaviours and worse clinical outcomes. Timely discussions must be held between MDST professionals and young people to improve their awareness of long-term co-morbidities, which may be reduced by modifying lifestyle factors (such as healthy eating, regular exercise, avoidance of smoking and limiting alcohol intake) as well as optimal adherence to treatment regimes.

Conclusion

The holistic care of children and young people with complex, chronic

rheumatic disorders is by definition complex and challenging. Identification and management of co-morbidity in paediatric rheumatic disease is increasingly becoming important with improving medical therapies and approaches to treatment. Novel therapies including biologic agents provide significant opportunity to improve quality of life and long-term prognosis. By raising awareness of the importance of co-morbid conditions this review aims to focus and direct paediatric and adult rheumatologists to address their current care and practice. Potential complications and co-morbid conditions arising from these disorders and their treatment regimens require specific attention at an early stage, especially as clinical effects may only be apparent in the distant future. It is therefore imperative that we consider co-morbidities sooner rather than later in order to further improve long-term patient outcomes. Lifestyle issues are likely to be important and need to be addressed in generic health advice. Specific challenges to overcome the paucity of an evidence base to direct care of these co-morbid conditions must be addressed to determine optimal standards of care for comorbid disease prevention. This requires proactive national and international collaborative efforts of researchers across different disciplines in prospective, long-term, collaborative follow-up studies.

Key messages

- Identification of co-morbidity is increasingly important with improvements in the prognosis of underlying paediatric rheumatic diseases.
- The evidence base underpinning co-morbidity management must be addressed to determine optimal standards of care.

- Long-term observational studies spanning the transition period are key to addressing these issues.

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