Pulmonary hypertension in juvenile-onset systemic lupus erythematosus: a case series

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Abstract

Objective

Systemic lupus erythematosus (SLE) is a rare multisystem autoimmune disorder with a variable clinical phenotype. Pulmonary hypertension (PHTN) is a recognised (and not uncommonly asymptomatic) complication of the condition with an associated poor prognosis in adults. It is relatively rare in juvenile-onset SLE (JSLE).

Methods

We present a retrospective descriptive case series of four female children aged 4 to 15 years at presentation of JSLE and aged 8 to 27 years at time of diagnosis of PHTN from the United Kingdom. All cases were identified through the UK JSLE Cohort Study.

Results

Of 665 children with JSLE in the UK cohort study to date (data from 2006–2020), four (0.6%) were identified as having PHTN. 3/4 of the PHTN cases presented with cardiovascular symptoms and / or signs at presentation. 3/4 were treated with Rituximab and had a good long-term outcome. Shared clinical features include high baseline disease activity scores.

Conclusion

JSLE has a high associated cardiovascular morbidity and mortality and early identification of treatable complications such as PHTN is vital. We suggest that children with high baseline disease activity scores and those presenting with cardiovascular symptoms and signs are most likely to have concurrent PHTN. Routine echocardiography is an effective screening tool and should be used as part of a standard diagnostic work-up.

Key words

juvenile systemic lupus erythematosus, pulmonary hypertension, vasculitis, paediatrics

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Introduction

PHTN is defined through direct right heart catheterisation as a mean pulmonary arterial pressure (PAPm) ≥25 mmHg at rest (1). In the context of SLE, pulmonary pressures rise due to a combination of pulmonary vascular inflammation, thrombosis and arterial vasoconstriction (2).

Juvenile onset SLE is a rare, severe and chronic multisystem autoimmune disease with an estimated incidence of 0.3–0.9 per 100,000 children-years (3). Around 20% of SLE is diagnosed in childhood. It is more common in females with the average age of onset occurring between 12–14 years (4). The standardised mortality rate for patients with SLE is 2.2 across all ages, and higher still (6.5) in children diagnosed with the condition (5). Compared to the adult-onset disease, JSLE is more a more aggressive condition with a higher incidence of cardiovascular, renal and neuropsychiatric complications (6).

PHTN is a rare complication of SLE, described in 1–14% of patients (7). In children, prevalence data from epidemiological studies suggests that the condition affects 4 to 10 cases per million per year (8). The majority of these cases arise in the context of chronic lung disease, congenital cardiac disease and persistent primary PHTN, with a smaller subset related to connective tissue disorders such as SLE and systemic sclerosis (in the latter, estimated to affect approximately 10% of adult patients with the condition) (9, 10). Connective tissue disease is the most commonly identified type of disease-associated PHTN in adult patients (11). In the largest paediatric PHTN registry, 3% of cases were related to connective tissue diseases (12).

A UK cohort study of adult patients diagnosed with PHTN over a 5.5-year period across five specialist centres reported 35 cases (8% of the cohort) with SLE-associated disease (13). A prospective study of SLE patients (66 adult, 8 paediatric) used echocardiography to diagnose PHTN (peak tricuspid valve systolic pressure gradient >30 mmHg) in 11% of the cohort (including one 12-year-old). In this particular study, there was no correlation found between pulmonary pressures and markers of disease activity (for example ESR, Disease Activity Index score) (14).

Adults with SLE are at substantially increased risk of cardiovascular morbidity and mortality (15–18). PHTN is associated with a particularly poor prognosis with three-year survival of 89% (19, 20). Importantly this complication is not always clinically evident with reports from prospective studies quoting asymptomatic disease in 18% of cases (21, 22).

Young females with a diagnosis of SLE for 5 years or more, and those with higher levels of disease activity (in particular those with serositis, lupus nephritis, cutaneous involvement) appear to be at greater risk of developing PHTN (22-25). There are also some key immunological features that have been associated with the condition (presence of rheumatoid factor and antiphospholipid and anticardiolipin antibodies for example) (24). There are very few biomarkers clinically validated for use in SLE currently, but many under investigation (for example soluble CD14 and syndecan-1 in lupus nephritis) (26) which perhaps will help in the quest for early detection of complications such as PHTN in future.

In JSLE, comprehensive epidemiological data on PHTN is lacking. Estimates of its prevalence (as a sub-clinical entity) have been reported at 2% for those with milder SLE presentations (27). Within this large cohort study, it was noted that there was a higher prevalence of serositis and fever in the children identified as having PHTN.

Methods

We report on a retrospective case series of children in the UK with Juvenile-onset SLE (JSLE) complicated by pulmonary hypertension. All cases were identified through the UK JSLE Cohort Study (data collected from 2006 onwards) (28). Clinical data was extracted through use of a standardised proforma (patient demographics, comorbidities, presence/absence of lupus nephritis, family history of autoimmune disease, clinical signs of PHTN, echocardiography results, immunology, treatments, EULAR (European

League against Rheumatism/American College of Rheumatology) and SLE-DAI (Systemic Lupus Erythematosus Disease Activity scores) (29). The 2019 EULAR/ACR classification criteria were used for diagnosing JSLE (30). Pulmonary hypertension was diagnosed through assessment of mean pulmonary artery pressure using echocardiography with or without cardiac catheterisation. Where mentioned, functional classification of PHTN was according to the World Health Organisation (WHO) criteria (31).

Results

Of 665 children with SLE in the UK cohort study to date, four were identified as having PHTN (0.6% of cohort). One patient was diagnosed with PHTN after the age of 18 years. The clinical characteristics of each case are summarised in Table I.

Manifestations of JSLE in this case series included haematological abnormality (2/4), lupus nephritis (1/4), musculoskeletal (3/4) and neuropsychiatric disorders (1/4). PHTN was identified at an interval of between two months to twelve years from JSLE diagnosis.

Our first case (8 years, female) presented with a prodrome of fatigue, myalgias and weight loss over an 18-month period. This was followed by a more rapid decline in her health (reduced exercise tolerance, retrosternal chest pain). She was found to have hepatosplenomegaly and generalised lymphadenopathy on initial examination with marked cytopenia and immunology confirming a diagnosis of JSLE after exclusion of haematological malignancy with a bone marrow aspirate and lymph node biopsy. Her cardiovascular examination revealed a loud second heart sound. Further assessment with echocardiography revealed severe PHTN (right ventricular systolic pressure (RVSP) estimated at 79 mmHg). Cardiac MRI was performed which confirmed right ventricular hypertrophy and dilatation of the pulmonary arteries. She received high dose intravenous methylprednisolone (30 mg/kg/dose over 3 consecutive days) and intravenous rituximab (750 mg/m^2/dose for 2 doses) followed by oral mycophenolate mofetil (MMF, 600 mg/m^2/dose twice daily) and Hydroxychloroquine (100mg once daily). Her pulmonary pressures improved after treatment initiation (moved from WHO functional class II to WHO class I) (31). She commenced treatment with sildenafil (20 mg three times daily) and her clinical course has been one of steady improvement and disease stability over subsequent reviews.

Our second case (9 years, female) presented with weight loss, intermittent fever, malaise, myalgias and rash in the year prior to her diagnosis. Clinical features included malar rash, cervical lymphadenopathy and heavy proteinuria (>0.5 g protein/day) at initial presentation. Immunological testing confirmed her diagnosis and she commenced oral prednisolone (1mg/kg/day) and hydroxychloroquine (6.5 mg/kg/dose once daily). Her proteinuria progressed and she underwent percutaneous renal biopsy which identified ISN/RPS Class III lupus nephritis. She commenced oral MMF (600mg/m^2/dose twice daily) and anti-proteinuric therapy with an angiotensin converting enzyme inhibitor (ACEi). Her disease activity remained significant despite these measures and she went on to receive treatment with intravenous rituximab (2 doses at 750 mg/m^2/dose) and intravenous cyclophosphamide (500 mg/m^2/dose) for separate 'flares'. As part of her routine assessment, echocardiography revealed mild PHTN (tricuspid regurgitation with Vmax 3.9 m/s). She experienced episodes of intermittent retrosternal chest pain and was noted to have clinical examination findings consistent with pulmonary hypertension (loud second heart sound, parasternal heave).

Our third case (female, 4 years) presented very acutely with cardiac, bone marrow and neurological disease (seizures) from the outset, necessitating intensive care admission. Initial treatment involved significant immunosuppressive therapy (high dose intravenous methylprednisolone (30 mg/kg/dose for 5 doses), intravenous cyclophosphamide (500 mg/m^2/dose for 5 doses) and 5 sessions of plasmapharesis). She received a second course of intravenous methylprednisolone (30 mg/kg/dose for 3 doses) followed by oral MMF (600 mg/m^2/dose twice daily) to manage a subsequent disease flare. Two years later she developed chest pain and exertional dyspnoea with echocardiography and cardiac MRI demonstrating right ventricular hypertrophy. Cardiac catheterisation was performed which confirmed PHTN (resting pulmonary artery pressures MAP 39 mmHg). She went on to receive treatment with intravenous rituximab (750 mg/m^2/dose for 2 doses) noting that her inflammatory markers remained high (ESR 92 mm/hr). Her disease has remained quiescent since

Our fourth case (female, 15 years) presented with high fever, myositis and rash following a 12-month prodrome of fatigue, weight loss and poor exercise tolerance. Early investigation with echocardiography and spirometry revealing a moderate pericardial effusion and restrictive lung disease (forced expiratory volume over 1 second (FEV1) 60% of predicted, forced vital capacity (FVC) 60% of predicted, transfer capacity of the lung for the uptake of carbon monoxide (TLCO) reduced at 56% of predicted). She was diagnosed with a juvenile dermatomyositis / lupus overlap syndrome. Immunology confirmed ANA, anti-Sm and anti-RNP antibody positivity. She responded well to high dose intravenous methylprednisolone (30 mg/kg/dose for 3 doses) and subcutaneous methotrexate (MTX, 25 mg weekly) initially and due to her stability over several years her MTX was discontinued and she was managed solely on hydroxychloroquine (5 mg/kg/dose once daily). More latterly her disease flared, requiring treatment with Prednisolone and MMF (she has continued on the latter at 600 mg/m^2/dose twice daily). The diagnosis of PHTN (echocardiography identified a pulmonary artery systolic pressure of 26 mmHg and mild tricuspid regurgitation) came some 12 years after her initial presentation. Her symptoms included exertional dyspnoea and dizziness with clinical examination noting the presence of a prominent second heart sound. She has not required any specific treatment for her PHTN, which has gradually improved over a 2-year period.

Table I. Patients identified from the UK JSLE National Lupus Registry.

	Case 1	Case 2	Case 3	Case 4
Sex	Female	Female	Female	Female
Age at diagnosis of SLE (years)	8	9	4	15
Age at diagnosis of PHTN (years)	8	13	12	27
Ethnicity	White (European)	Black African	White (European)	Black Other
Comorbid conditions	Autoimmune hypothyroidism	Sickle cell anaemia	Nil	Raynaud's phenomenon; Migraine; Hidradenitis
Lupus nephritis?	No	Yes – class III on biopsy, sub-nephrotic range proteinuria, normal renal function	No	No
Family history of autoimmune disease	Yes (father = vitiligo)	No	Yes (mother = SLE)	Yes (father = RA)
Signs and symptoms of PHTN	Chest pain; reduced exercise tolerance; loud P2 heart sound.	Incidental finding on routine screening echocardiogram.	Chest tightness; shortness of breath.	Shortness of breath at rest; reduced exercise tolerance; dizziness; syncope; loud P2 heart sound.
Echocardiography findings	RVSP = 79 mmHg + RAP	RVSP = 60 mmHg + RAP	No specific concerns on ECHO. Cardiac catheterisaton confirmed diagnosis.	Pulmonary artery systolic pressure = 26 mmHg
Immunology	ANA Anti cardiolipin antibodies Anti-Smith antibodies Anti RNP positive	ANA Anti dsDNA Low C3	ANA Anti dsDNA Low C3	ANA (1: 640) Anti RNP positive Anti-Smith antibodies
Anti-Smith antibodies	Yes	No	No	Yes
Complement	Developed PHTN 2 months following diagnosis. At this point, C3 was lower than previous (0.97 *vs*. 1.29 g/L).	Low C3 (0.77) at diagnosis of PHTN	Low C3 0.79 at presentation. Was reported as in the normal range when diagnosed with PHTN	C3 1.07 at time of diagnosis of PHTN
Treatment and change in response to PHTN diagnosis	Sildenafil added. Pulsed MP; addition of MMF; Rituximab	Sickle cell optimisation. Received rituximab and cyclophosphamide x 2	Almlodipine started. Rituximab. MMF increased to 700 mg BD.	No additional treatment.
EULAR score	24	27	27	21
SLEDAI score	10	21	20	11

ANA: antinuclear antibodies; PHTN: pulmonary hypertension; RA: rheumatoid arthritis; RAP: right atrial pressure; RVSP: right ventricular systolic pressure; SLE: systemic lupus erythematosus; Anti RNP: Anti-ribonuclear protein antibodies; EULAR: European Alliance of Associations for Rheumatology (a new classification criteria for SLE, using ANA positivity as an entry criterion and then weighted criteria in 7 clinical and 3 immunological domains (those scoring ≥10 are classified); SLEDAI: SLE Disease Activity Score (score at time of enrolment).

Discussion

We have described the clinical features of four cases of JSLE complicated by PHTN from the UK between the years 2006 and 2020. SLE and PHTN *per se* are rare conditions in childhood and the combination of the two is even rarer. There is very little published data on this particular complication of JSLE. It is clear from adult studies that it has a significant associated morbidity and mortality and is therefore important to identify at an early stage.

Acute cardiac complications of SLE have been shown to be more common in children compared to adults. Chang *et al*. (32) identified an acute cardiac diagnosis (myocarditis/pericarditis/valvular dysfunction) in 17.8% of 197 children with new onset SLE, with incidence highest in the first year after diagnosis. In this study, African-American race and lupus nephritis were significantly associated with an acute cardiac diagnosis and childhood onset disease was associated with a 4.4-fold higher rate of acute cardiac disease when compared to adults.

Recommendations published by the Single Hub and Access Point for paediatric Rheumatology in Europe (SHARE) in 2017 include baseline echocardiography/ECG and intermit-

tent monitoring for future progression/new involvement of the cardiopulmonary system, in order to reduce the chance of subsequent organ damage in children diagnosed with SLE (33).

Based on our observations, we would consider there to be a heightened risk of PHTN in children who present with high disease activity scores (and therefore should be assessed for at the point of initial presentation), perhaps more so in the presence of certain immunological markers (anti-cardiolipin and anti-RNP antibodies). This is consistent with published literature in which a high score (defined as SLEDAI greater than or equal to 10) has been associated with greater exposure to steroids and damage accrual over a median follow-up period of 5.1 years (34). Cardiorespiratory clinical symptoms and signs were observed in 75% (three of four) cases and should prompt urgent echocardiography and where possible, consideration of cardiac MRI to facilitate a timely and accurate diagnosis of PHTN.

We consider there to be a possible role for intravenous rituximab in treating the PHTN associated with SLE and note that of the three patients who received this treatment, all have gone on to do well clinically. A 2008 case report describing a young patient with JSLE complicated by PHTN, presented data to suggest that intravenous rituximab had been important in facilitating resolution of the PHTN (35). Zamanian *et al*. showed the efficacy of intravenous rituximab for treating the PHTN associated with systemic sclerosis in 2021 (36).

It seems likely that we are underestimating the prevalence of PHTN in our UK cohort of children with SLE. The Anuardo *et al*. 2017 large Brazilian cohort study (27) showed a 2% (17 / 852) prevalence of PHTN in JSLE. The majority (78%) of the 852 identified were asymptomatic. Of the symptomatic cases, 18% (3 of 17) presented with exertional dyspnoea and 6% (1 of 17) with chest pain. In this study, reticuloendothelial manifestations, fever and serositis were significantly more likely in those patients identified as having PHTN. Disease activity scores, antiphospholipid antibody syndrome, neuropsychiatric and renal manifestations did not differ between those with and without PHTN.

In conclusion, we support the role of routine echocardiography for children diagnosed with SLE. SLE is a condition associated with significant long-term cardiovascular morbidity and mortality and therefore early identification and treatment of acute cardiac conditions is of the utmost importance. By adding this descriptive case series to the current literature on this rare condition, we also hope to improve the initial risk stratification of patients with JSLE with the ultimate goal of improving the precision of treatment algorithms and consequent clinical outcomes.

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