Juvenile Idiopathic Inflammatory Myopathy at a developing Paediatric Rheumatology Clinic in Trinidad and Tobago: a case series

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Abstract

Objective:
Juvenile Idiopathic Inflammatory Myopathy (JIIM) is a rare autoimmune disorder with no published data from the English-speaking Caribbean. As such, we seek to produce the first dataset from Trinidad and Tobago on this condition.

Methods:
Clinical notes of patients with JIIM, who attended the recently formed Paediatric Rheumatology Multi-Disciplinary Clinic over a 6-month period at the San Fernando Teaching Hospital were analysed. Clinically inactive disease at last visit was also assessed from the patients' notes.

Results:
5 patients clinical records were reviewed in this period. 4 were female and average age of onset was 6.8 years. 4 cases were Juvenile Dermatomyositis (JDM). The most common presenting complaints were skin rash and weakness whilst the most common additional symptoms were joint pains and pruritis. 2 patients had previous upper respiratory tract infection. Creatine Kinase was extremely elevated in one patient with juvenile polymyositis. 3 were positive for Antinuclear Antibodies. 2 patients were positive for Extractable Nuclear Antigen antibody (RP155). 3 patients utilized MRI which detected myositis in all reports. Oral medications included methotrexate and prednisolone. Parenteral drugs used included intravenous immunoglobulin and methylprednisolone. 4 patients had vitamin D supplementation and all 5 were prescribed physiotherapy. 2 had clinically inactive disease at last visit.

Conclusions:
This represents the first case series of JIIM in the English -Speaking Caribbean. Recommendations from this study include greater utilization of MRI in diagnostic workup and further evaluating anti RP155 antibody as a possible myositis associated antibody.

Introduction

Juvenile Idiopathic Inflammatory Myopathy (JIIM) is considered a group of rare autoimmune diseases characterised by muscle weakness and characteristic skin rashes. [1] Of the various subtypes of JIIM, Juvenile Dermatomyositis (JDM) is the most common and accounts for approximately 80% of all JIIM. The incidence reported in the literature is estimated to be 2-3 per million. [1]

Over the last two decades, there has been a magnitude of research into causation, associations and pathophysiology of JDM. [1,2,3] The current thinking is environment plays a key role in a genetically susceptible host. [2] There is evidence of an inverse relationship of latitude and prevalence of JDM in European cities. [3] However, there is currently no published evidence on JIIM in Trinidad and Tobago, nor in the English-speaking Caribbean.

In the twin island of Trinidad and Tobago, there are five Regional Health Authorities serving a population of 1.4 million people. They are North West, North Central, Eastern, South West and the Tobago Regional Health Authorities. The South West Regional Health Authority (SWRHA) serves an estimated catchment of 600 000 people and there is one tertiary centre for paediatrics. Of note, there are no double qualified Paediatric Rheumatologists at present. As such, all paediatric rheumatology patients are seen under General Paediatrics with consultation and input from the Adult Rheumatology service.

In February 2021, a decision was made to establish a Multi-Disciplinary Paediatric Rheumatology Clinic at SWRHA, with an aim to optimise care for these children. Here, children up to 18 years would be seen together by both Paediatric Medical and Adult Rheumatology with an aim to enhance the care for children with rheumatological conditions. Thus, the few paediatric rheumatology patients at the SWRHA have been brought into one clinic. Preliminary analysis of these patients revealed that together with lupus, JIIM had the highest number of cases in the clinic (unpublished data). With this background, the present study determined to analyse the characteristics including investigations and outcomes of this JIIM population at this single institution.

Methods

After obtaining ethical approval from the Bioethics Committee of the South West Regional Health Authority; a retrospective chart review was undertaken on the clinical characteristics of JIIM/JDM patients at the San Fernando Teaching Hospital over a 6-month period.

Inclusion criteria were:

a. Children less than eighteen years
b. Attending the Paediatric Rheumatology Multi-Disciplinary Clinic of South West Regional Health Authority
c. A diagnosis of possible, probable or definite idiopathic inflammatory myopathy or a diagnosis of possible, probable or definite juvenile dermatomyositis

Only patients' clinical files who attended this clinic during the period from May to October 2021 were analysed. The information was extracted and entered into Microsoft Excel™ from which data analysis was done and descriptive statistics reported.

Demographic data, month of presentation and time lag between symptom onset and presentation were analysed. Additionally, examination findings, laboratory and diagnostic investigations were extracted from the notes. The number of relapses and also immunosuppressive drugs used in management of these children with JIIM and JDM were examined. In addition, utilisation of physiotherapy, skin protection and vitamin D supplementation were also recorded along with calcinosis treatment.

We also assessed if patients had clinically inactive disease, at the last visit, based on a modified Paediatric Rheumatology International Trials Organisation (PRINTO) Criteria following a previous study published from South Africa by Okongo *et al*. [4,5]

Our criteria included a Childhood Myositis Assessment Score (CMAS) > 47 and a serum Creatinine Kinase >150 U/L.

Table 1. Characteristics of patients with JIIM

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
Gender	Female	Female	Male	Female	Female
Age at presentation	5years	10years	2years	6 years	11 years
Clinical presentation	Rash x 2years; Weakness in limbs x 2 months Weight loss x 2 months Joint pains, weakness, fever, fatigue	Joint pains x 3 weeks Rash x 4 weeks Joint pains, pruritis	Rash x 1 month Intermittent fever Weakness to stand Joint pains, weakness, fever, pruritis, diarrhea	Weakness in legs x 2 months Weakness, fatigue, falls	Dark patches on skin Pruritis, dysphagia
Additional symptoms on presentation					
Past medical history	Lichen Striatus	Kawasaki Disease at 4 years of age	Nil	1. LRTI 2010; 2. Constipation 2013	Asthma
Key risk factors (infections in last 6 months, social stressors, autoimmune history)	Nil	Exam stressor Recent upper respiratory tract infection	Recent upper respiratory tract infection	Nil	Family history of Rheumatoid Arthritis
Skin findings: Heliotrope rash, Gottron's Sign, Gottron's Papule	Yes	No	Yes	Yes	Yes
Calcinosis present	Nil	Nil	Yes	Nil	Nil
Diagnosis	JDM	JPM	JDM	JDM	JDM

LRTI- Lower respiratory tract infection, JDM- Juvenile dermatomyositis, JPM- Juvenile Polymyositis

Results

A total of five (5) patients' clinical notes were reviewed in detail during the study time-period. Of these, 4 were JDM and 1 was juvenile polymyositis (JPM). See Table 1 .

Of all patients, 4 were female and 1 was male. The age at presentation ranged from 2 years to 11 years. Average age at presentation was 6.8 years with a median of 6 years. No clusters were seen in terms of location of these children.

Whilst 2 patients had their first symptom in November, there was no observable pattern of month of presentation. The average time lag between first symptom and presentation was 3.8 months.
The most common presenting complaint were skin rash and weakness followed by joint pains, fever and weight loss.

The most common additional symptom was joint pain in 3 and pruritis in 3; followed by fever in 2 and fatigue in 2. One patient with 5 additional symptoms was male and presented at 2 years of age.

Four children had some documentation of muscle weakness on examination. In terms of skin findings, 4 had documented pathognomonic changes of JDM of which, Gottron's papule was the most common pathognomonic skin finding.

In terms of environmental factors, 2 had previous infections in the 6 months prior to presentation. In addition, 1 had the potential stressor of entering final year of primary school. 4 had previous medical conditions which included: Kawasaki disease, asthma, lichen striatus and constipation. None had any systemic autoimmune conditions that could contribute to JIIM. Of note, 1 child had a positive family history of rheumatoid arthritis. See Table 1.

In terms of muscle enzymes at time of diagnosis, 3 had both elevated Creatinine Kinase (CK) and Lactate Dehydrogenase (LDH); 3 patients had elevated Alanine Transferase and 2 had elevated Aspartate Aminotransferase. 2 patients had missing LDH in the notes. The highest CK was 5950 U/L, documented in one child with JPM. (Reference Range for CK in females 9-11years: 52-256 U/L).[6]

With respect to autoantibodies, 3 had Anti-Nuclear Antibody (ANA) positivity documented. In 4 patients, Extractable Nuclear Antigen (ENA) were done. 3 out of 4 ENA were positive. Positive ENA autoantibodies included: Mi2A, Mi2B, RP11, RP155, PM75 and Ku. 2 patients were positive for RP 155.

Magnetic Resonance Imaging (MRI) of the thigh
There were 4 MRI of the anterior and posterior bilateral thigh muscles documented in the notes of 3 patients. All 4 MRI identified muscle inflammation on short tau inversion recovery sequence reported by specialist radiologists. Features of myositis included oedema and high T2 signalling. One child had a repeat MRI done as a tool to measure response to escalated therapy which showed improvement, in comparison with the previous MRI done 42 months earlier.

Electromyography (EMG)
3 patients had EMG done. One EMG was able to identify acute myositis. One suggested a proximal myopathy with a coexisting neuropathy and one suggested inflammatory myopathy but thought the pattern was non-specific and other aetiologies should be considered.

Muscle Biopsy
3 out of 5 patients had muscle biopsies. 2 were reported as non-specific features and one as connective tissue elements only. Due to issues with access, training and resources the rle of muscle biopsies in this setting is unclear.

Immunosuppressive drugs used
All patients received steroids and methotrexate. Parenteral drugs included: Intravenous Immunoglobulin and methylprednisolone. At the time of collection of data, 2 were on more than one immunosuppressant therapy other than prednisolone. One child had calcinosis in this dataset. He was on 5 immunosuppressive therapies simultaneously, whilst on prednisolone. His response to calcinosis treatment was unsatisfactory and he was treated with adjunctive therapies like diltiazem, colchicine and intralesional steroids.

Disease activity
In assessing inactive disease, we looked at the last documented CMAS > 47 and CK levels <150 U/L. 3 patients had CMAS > 47 and 3 had CK less than 150 U/L at the last visit. However, only 2 patients met both criteria for inactive disease.

Additional treatment
Four patients had vitamin D and calcium supplementation, 3 had sunscreen or protective clothing documented and 5 had physiotherapy prescribed.

Disease flares number and type
Three patients had documented flares. 1 child had four flares- two of which were skin and two were muscle weakness. The other 2 children had one muscle weakness flare.

Physical manifestations
Three patients had physical changes at last visit. These included alopecia, muscle atrophy, abdominal pain, contractures, calcinosis and growth failure. No patient had any lung changes documented. One child had difficult to treat calcinosis.

Additional investigations
No structured screening programme for JIIM complications was being done. As such, patients had neither echocardiography, spirometry nor chest computerized tomography. Three patients had ECGs, which were normal. Chest X-ray documentation of lung

changes were not seen.

Discussion

JIIM is rare but is a well-known entity. The number of patients enrolled in this study was only five and as such it would be difficult to make any general statements on prevalence or incidence in this population. However, it is important to enhance this dataset and encourage further research to better define the clinical trends and treatment outcomes in the Caribbean population.

We did see a female predominance in our study which is in keeping with most of the international literature on this disease. [7,8] Additionally, the peak age of onset is approximately 7 years [7,8] and we found an average of 6.8 years with a median age of 6 years in our study. Whilst it is recognized that there is an increasing prevalence as one moves closer to the equator, as well as increased flares in exposure to increase UV radiation, [2,3] our dataset did not reveal any specific month of presentation or onset of disease. Meteorological data would be required to compare UV radiation in each month to make an objective assessment with a larger sample size.

In terms of environmental triggers, 2 out of 5 had a previous upper respiratory tract infection in 6 months prior to presentation which is a recognized trigger for disease flares in children with JDM. [2] Interestingly, there was one patient who had a past medical history of Kawasaki disease which is now a recognized risk factor for autoimmunity. In a 2020 registry-based cohort study by Danish researchers, patients with previous Kawasaki disease had an increased risk of developing autoimmune diseases including dermatomyositis and polymyositis after 10 years of the disease. [9] Of note, this patient developed JIIM, 6 years after presenting with Kawasaki disease. This should make us rethink the long term follow up of Kawasaki disease - beyond just its cardiac sequelae. A recommendation would be to refer these children to the rheumatology service as is done in Singapore. [10]

The most common presenting complaint were skin rash and weakness and joint pain and pruritis were the most common additional features present. The range of varying symptoms highlights the fact that JIIM can present with many other constitutional features. [7] In terms of pathognomonic features, Gottron's papule and heliotropic rash were the most present feature in our JDM patients, which is usually the findings that help distinguish JDM from JPM. [11]

Of note, with respect to muscle enzymes, the highest CK was found in the one child who had JPM. This is in keeping with the fact that CK in JIIM patients tend to be higher in JPM compared to JDM. [11] This study found a 60% ANA Positivity rate which is similar to the 70% reported by Shah *et al.* [11]

Myositis Specific antibody panels and Myositis Associated Antibodies panels are not available in the public setting at SWRHA and may account for the low testing seen in the notes reviewed. However, a few notable observations on autoantibodies done from Extractable Nuclear Antigen-23 testing was discovered.

Anti p155/140 also known as transcriptional intermediary factor 1- gamma, which is the most common autoantibody in JDM, was not found in this dataset. [1] One child with JDM, tested positive for Anti PM and Anti Ku which can be found in myositis and systemic sclerosis overlap. [12] Another patient with JPM, was positive for Anti RP155 only, which is not one of the usual autoantibodies as identified by Rider and Nistala in their comprehensive overview. [1] One patient with JDM tested positive for four Autoantibodies which included: Anti Mi2 A, Anti Mi2 B, Anti RP11 and Anti RP155. Anti Mi2 is well documented as a myositis specific antibody, however, Anti RP11 and RP155 can be associated with systemic sclerosis. [13] As such, it raises the question whether these two children with Anti RP155 positive Antibodies, may have JDM overlapping with another connective tissue disease, sometimes termed "overlap myositis". [1,14] It may also be possible that this is a new autoantibody association of JDM in a Trinidadian population. However, the study size was too small to definitively pronounce that Anti RP155 is a new myositis associated antibody in a Trinidadian population.

It is noteworthy that MRI was utilised in 60% of patients, as it offers the advantage of being non-invasive and is now being utilized more frequently in diagnostic workup as well as in monitoring response to therapy in JIIM. [15,16] Specifically, in our study, muscle biopsy and EMG was

documented in 60% of patients, which could be due to the invasiveness of these procedure. Moreover, muscle biopsy did not add much information to the diagnosis in this case series. Additionally, this institution does not have specialized histopathology services available to effectively report on JIIM specimens. Whilst it would be beneficial to have trained personnel to offer this service, MRI may offer an interim solution to assist in diagnosis. As such, earlier use of MRI should be considered in the diagnostic work-up of these patients.

The diagnosis of JDM has long been based on the works of Bohan and Peters in 1975. [17] Although it still remains widely in use by residents and clinicians across the board, there have been many attempts to revamp this criterion, with the latest being the EULAR/ACR Classification of 2017. [18] The advantage of this new criteria is that it can be scored with or without a muscle biopsy recognising the shift away from invasive testing. Additionally, there is an online calculator which facilitates an easier scoring. [19] Leclair and Lundberg compared sensitivities and specificities of six varying IIM criteria and found that, when compared to Peter and Bohan's criteria, EULAR/ ACR 2017 had a slightly lower sensitivity (87- 93% compared with 94 -98%) but much better specificity (82 - 88% compared with 29-55%). [20] As such, we recommend that the EULAR/ACR 2017 classification criterion be utilised in our setting, as EMG and Muscle Biopsy did not add diagnostic benefit.

The treatment options in this case series were in keeping with current guidelines. [21] With respect to clinically inactive disease at the last visit, we used a modified PRINTO criteria similar to that used by O'kongo *et al.* [4] 40% had clinically inactive disease by our criteria of analysis whilst on methotrexate and prednisolone only. Three patients had physical manifestations of JIIM at their last visit. One patient had calcinosis in this dataset. His calcinosis appeared to be unresponsive to multiple therapy. Of note, there is no established guideline on JDM calcinosis management in the literature, however a survey of paediatric rheumatologists in 2017, found that optimising immunosuppressants and adding adjunct therapies like bisphosphonates and calcium channel blockers were the top two additional therapies recommended. [22] A recommendation would be for this institution to look at establishing a protocol for adjuvant therapy- like bisphosphonates, in children with JDM as another option for intractable calcinosis.

One of the major limitations of this case series was that being retrospective in nature, the authors found several gaps existed in record-keeping.

Nevertheless, this case series highlighted the characteristics and outcomes of JIIM in a tertiary care teaching hospital in the Caribbean. The recently established Paediatric Rheumatology Multi-Disciplinary Clinic has created an opportunity for research into this subspecialty field. The analyses of the JIIM patients provided some useful insights. There was an important association of Kawasaki disease and future development of autoimmunity and hence it may be advisable that future patients with Kawasaki disease be offered rheumatology follow up. Moreover, because MRI offered a 100% ability to detect myositis, we recommend that this less invasive modality be utilised in this setting, instead of muscle biopsies which may be non-contributory. A higher proportion of Anti RP155 positive patients may indicate overlap myositis or the potential for a new myositis associated antibody in the Trinidadian JIIM population. We would also recommend establishing a new protocol for bisphosphonate treatment for difficult-to-treat calcinosis in JDM, given its underutilisation and rarity in the local population. Overall, this study highlights the first data published on JIIM from Trinidad. We recommend that a dedicated Paediatric Rheumatology Service may be essential to provide care in places where this subspecialty is underserved and/or underdeveloped.

LIST OF ABBREVIATIONS:

SWRHA- South West Regional Health Authority

EULAR- European Union League Against Rheumatism

ACR- American College of Rheumatology

PRINTO- Paediatric Rheumatology International Trials Organisation

CMAS- Childhood Myositis Assessment Score

JIIM- Juvenile Idiopathic Inflammatory Myopathy

JDM- Juvenile Dermatomyositis

JPM- Juvenile Polymyositis

MRI- Magnetic Resonance Imaging

EMG- Electromyography

ECG- Electrocardiogram

ANA- Anti Nuclear Antibody

ENA- Extractable Nuclear Antigen

CK- Creatinine Kinase

LDH- Lactate Dehydrogenase

AST- Aspartate Transaminase

ALT- Alanine Transaminase

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ZL- concept, design, data collection, introduction, methodology, analysis, results, discussion, conclusion

SA- Data collection

PC- Data Collection

HD- Senior review of paper.
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References

1. Rider LG, Nistala K. The juvenile idiopathic inflammatory myopathies:
pathogenesis, clinical and autoantibody phenotypes, and outcomes. *Journal of Internal Medicine*. 2016;280(1):24-38.

2. Mamyrova G, Rider LG, Ehrlich A, et al. Environmental factors associated with disease flare in juvenile and adult dermatomyositis. *Rheumatology (Oxford)*. 2017;56 (8):1342-1347

3. Hengstman GJ, van Venrooij WJ, Vencovsky J, Moutsopoulos HM, van Engelen BG. The relative prevalence of dermatomyositis and polymyositis in Europe exhibits a latitudinal gradient. *Ann Rheum Dis*. 2000;59(2):141-142.

4. Okong'o LO, Esser M, Wilmshurst J, Scott C. Characteristics and outcome of children with juvenile dermatomyositis in Cape Town: a cross-sectional study. *Pediatr Rheumatol Online J*. 2016;14(1):60.

5. Lazarevic D, Pistorio A, Palmisani E, et al. The PRINTO criteria for clinically inactive disease in juvenile dermatomyositis. *Ann Rheum Dis*. 2013;72(5):686-693.

6. Kleinman K, McDaniel L, Molloy M. The Harriet Lane Handbook 22nd Edition. Table 28.1 Reference values. Elsevier. 2021

7. Pilkington CA, Feldman BM, Sontichai W. Juvenile dermatomyositis and other inflammatory muscle diseases. In: Petty RE, Laxer RM, Lindsley CB, Wedderburn LR, Mellins ED, Fuhlbrigge RC. Textbook of Pediatric Rheumatology 8th edition. Philadelphia, Elsevier; 2021.

8. Harris W. Examination Paediatrics 4th Edition. A guide to Paediatric Training. Ch 16 Rheumatology. Juvenile Idiopathic Inflammatory Myopathies (JIIMs): Juvenile Dermatomyositis (JDM). Australia, Churchill Livingstone; 2011, 577- 586.

9. Nielsen TM, Andersen NH, Torp-Pedersen C, Søgaard P, Kragholm KH. Kawasaki disease, autoimmune disorders, and cancer: a register-based study. *Eur J Pediatr*. 2021;180(3):717-723.

10. Tan JHT, Fun HS, Arkachaisri T. Paediatrics Rheumatology Clinic Population in Singapore: The KKH Experience. *Proceedings of Singapore Healthcare*. 2012;21(4):265-271.

11. Shah M, Mamyrova G, Targoff IN, et al. The clinical phenotypes of the juvenile idiopathic inflammatory myopathies. *Medicine (Baltimore)*. 2013; 92(1):25-41.

12. Mahler M, Satoh M, Fritzler MJ. Anti-Ku antibodies: important points to consider. *Ann Rheum Dis*. 2021; 80

(11):e182.

13. Liaskos C, Marou E, Simopoulou T, et al. Disease-related autoantibody profile in patients with systemic sclerosis. *Autoimmunity*. 2017; 50(7):414-421.

14. Li D, Tansley SL. Juvenile Dermatomyositis-Clinical Phenotypes. *Curr Rheumatol Rep*. 2019; 21(12):74.

15. Corral-Magaña O, Bauzá-Alonso AF, Escudero-Góngora MM, Lacruz L, Martín-Santiago A. Juvenile Dermatomyositis: Key Roles of Muscle Magnetic Resonance Imaging and Early Aggressive Treatment. La resonancia magnética muscular y el tratamiento agresivo precoz, claves en la dermatomiositis juvenil. *Actas Dermosifiliogr (Engl Ed)*. 2018;109(6):e42-e46.

16. Thyoka M, Adekunle O, Pilkington C, et al. Introduction of a novel magnetic resonance imaging-based scoring system for assessing disease activity in children with juvenile dermatomyositis. *Rheumatology (Oxford)*. 2018;57(9):1661-1668.

17. Bohan A, Peter JB. Polymyositis and dermatomyositis. *N Engl J Med*. 1975;292(8):403-407.

18. Lundberg IE, Tjärnlund A, Bottai M, et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Ann Rheum Dis*. 2017;76(12):1955-1964.

19. Online Web calculator. Classification criteria for Idiopathic Inflammatory Myopathies. www.imm.ki.se/biostatistics/calculators/iim/.

20. Leclair V, Lundberg IE. New Myositis Classification Criteria-What We Have Learned Since Bohan and Peter. *Curr Rheumatol Rep*. 2018;20(4):18.

21. Bellutti Enders F, Bader-Meunier B, Baildam E, et al. Consensus-based recommendations for the management of juvenile dermatomyositis. *Ann Rheum Dis*. 2017;76 (2):329-340.

22. Orandi AB, Baszis KW, Dharnidharka VR, Huber AM, Hoeltzel MF; CARRA Juvenile Myositis subgroup. Assessment, classification and treatment of calcinosis as a complication of juvenile dermatomyositis: a survey of pediatric rheumatologists by the childhood arthritis and rheumatology research alliance (CARRA). *Pediatr Rheumatol Online J*. 2017;15(1):71.