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ORIGINAL ARTICLE

Ulcerated lesions as a risk factor for Henoch-Schonlein purpura nephritis

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Objective

To determine the correlation between the severity of Henoch-Schonlein purpura skin manifestations and development of nephritis and to characterise the disease within the Maltese paediatric population.

Design

A retrospective analysis of the 96 cases diagnosed with Henoch-Schonlein purpura at Mater Dei Hospital between January 2008 and January 2016. Clinical notes were reviewed and anonymised data regarding the presentation, progression and follow-up of these cases was entered into a database.

Results

96 cases met the inclusion criteria with a male to female ratio of 1.35:1 and with a mean age at presentation of 6.4 years (interquartile range 3.5 years). 99% had the typical rash at presentation with 75% having other associated clinical findings. Renal involvement was found in 36.5%: isolated proteinuria in 19.8%, isolated haematuria in 13.5%, haematuria, proteinuria and hypertension in 3.1% and nephrotic range proteinuria in 2% of cases. A severe rash at presentation was shown to be a prognostic indicator for renal involvement.

Conclusion

Henoch-Schonlein purpura in the Maltese paediatric population is similar in incidence to that quoted in the literature. The majority of cases are uncomplicated and the outcome is frequently favourable. The presence of a severe rash at presentation significantly increases the risk of renal involvement and long term complications.

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INTRODUCTION

Henoch-Schonlein Purpura (HSP) is the commonest vasculitis in childhood with an incidence between 3-27 per 100,000 child population, with an increased prevalence in males.[1-2] It commonly presents between four and six years of age and is usually a self-limiting disease with rapid resolution of extra-renal symptoms. The long term prognosis correlates with renal involvement which involves about a third of cases. Chronic renal disease is estimated to occur in 1.8% of children and 10.4% of adults.[4] Reports have shown a difference in presentation between childhood-onset and adolescent-onset HSP, with the latter having increased incidence of musculoskeletal symptoms and a marginally increased risk of progression to end-stage kidney disease.[3] Korean and Japanese individuals also seem to have a higher prevalence of HSP as compared to other races.[4] There are a number of rare complications that can be associated with HSP including orchitis, cerebral and cerebellar haemorrhage and pulmonary haemorrhage.

Microscopically, the condition is characterised by the deposition of IgA immune complexes in the organ vasculature, hence its new nomenclature in the Chapel Hill classification, IgA vasculitis.[4,5,6] Common viral infections often precede the condition as demonstrated by a higher incidence in the winter months. Predisposed individuals have abnormal glycosylation sites on IgA1 antibodies. Viral upper respiratory tract infections and gastrointestinal infections lead to increased production of these abnormal IgA1 antibodies and these are recognised by circulating anti-glycan antibodies, leading to the formation of the circulating immune complexes with deposition in the organ vasculature.[7]

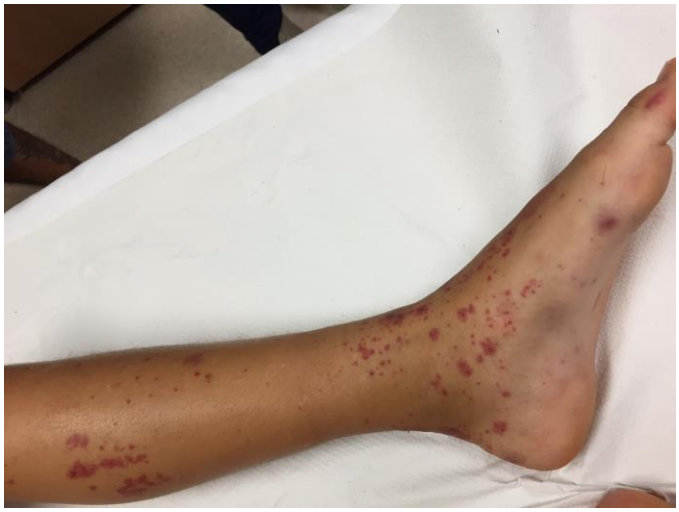
Laboratory tests at presentation commonly show raised inflammatory markers and IgA levels and a variable degree of haematuria and/or proteinuria.[8]

PATIENTS AND METHOD

The clinical notes of all patients aged less than 16 years (otherwise passed to adults) admitted with HSP to Mater Dei Hospital between January 2008 and January 2016 were reviewed. Data included demographics, clinical findings at presentation, laboratory test results and out-patient follow-up findings. All data was anonymised in a database.

We graded the severity of the rash as either mild, that is, a fine purpuric rash (figure 1), or severe, that is, palpable purpura with or without ulcerated lesions (figures 2 and 3).

Figure 1 Showing mild purpura



Blood tests were interpreted according to normal ranges for the patient's age and sex. HSP nephritis was monitored using urine dipstick and formal urinalysis and microscopy. Haematuria was defined as 1+ to 3+ on dipstick whilst proteinuria was defined as 1+ to 3+ or greater than 150mg/L on dipstick on three consecutive days. Proteinuria was quantified using the urine albumin: urine creatinine ratio. Nephrotic range proteinuria was defined as a

24hr urine protein of more than 40mg/m^2/hr whilst nephritic-nephrotic syndrome was defined as more than 200 red blood cells on urine analysis and 24hr urine protein of more than 40mg/m^2/hr and the presence of hypertension and/or biochemical findings of renal dysfunction. Blood pressure values were compared to age, sex and height-matched percentile values and hypertension was considered if the measured systolic and diastolic values exceeded the 95th percentile according to the Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents.[15]Recurrence of HSP was considered if a patient who was symptom-free for at least a month presented with fresh signs and/or symptoms related to HSP.

Figure 2 Showing more severe palpable purpura

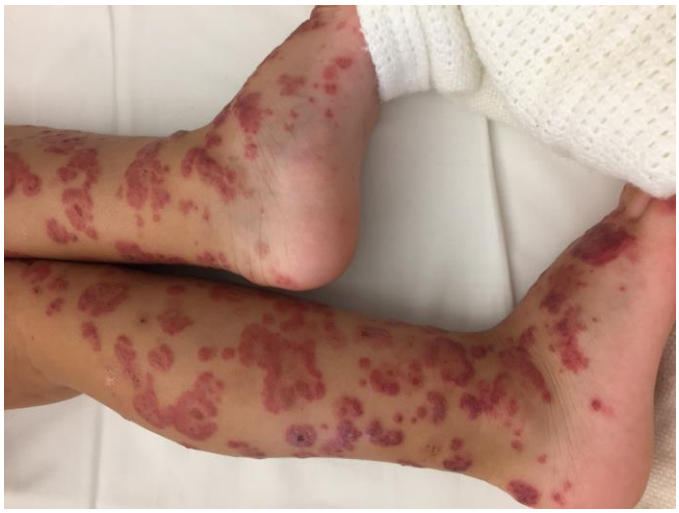
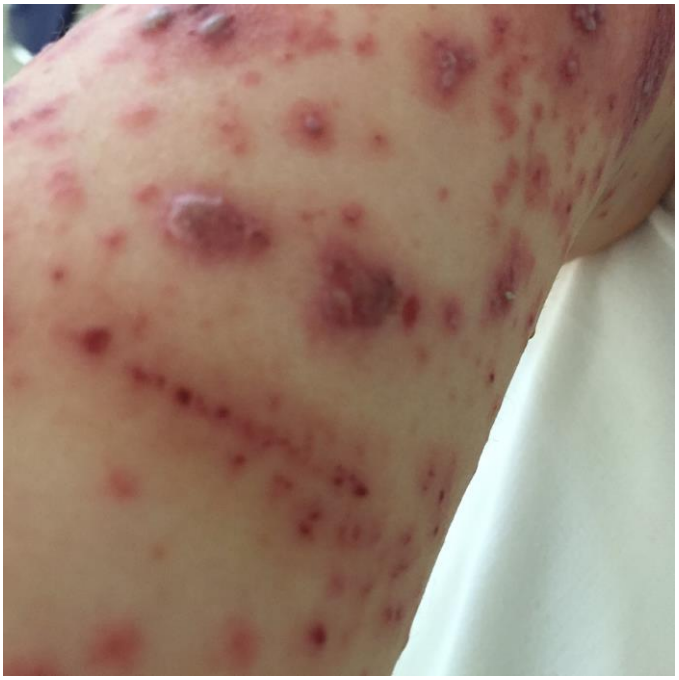


Figure 3 showing severe purpura with blistering and ulcerated lesions



Statistical analyses were performed using Microsoft Excel® 2010. Fisher Exact test was used to study the relationship between the severity of the skin rash and the presence of HSP nephritis.

RESULTS

Findings at presentation

96 children met the inclusion criteria. The male to female ratio was 1.35:1 with a mean age of 6.4 years (interquartile range 3.5 years). 65 cases (67.7%) presented in the months between September and March. A preceding infection, a mean of 2.8 weeks previously, was noted in 85 cases (88.5%), the majority being upper respiratory tract infections (82%).*Table 1 summarises the clinical findings at first presentation.*

95 children (99%) presented with the typical purpuric rash; one child presented with abdominal pain first, with the rash appearing within 3 days. Most children had a fine purpuric rash involving the lower limbs. 7 children

(7.3%) presented with palpable purpura whilst another 7 children (7.3%) had ulcerated lesions. The mean age of children presenting with mild purpura was 6.9 ± 2.3 years whilst the mean age of children presenting with severe purpura was 5.4 ±1.38 years p=0.0202 (CI 0.2392 - 2.76).

35 children (36.5%) had evidence of renal involvement within the first week of presentation: 19 (19.8%) had proteinuria and 13 (13.5%) had haematuria. Three children (3.1%) had a combination of haematuria ± proteinuria and hypertension at presentation. The clinical findings of the latter are shown in table 2.

Table 1 Summary of the signs and symptoms noted at first presentation

Clinical Signs And Symptoms At First Presentation		No. Of Cases	Percentage of Total (%)
Abdominal Pain		1	1
Typical Purpuric Rash		95	99
Type of Rash:	Fine purpuric Rash	82	85.4
	Palpable Purpura	7	7.3
	Ulcerated Purpuric Lesions	7	7.3
Rash distribution:	Mainly Involving Lower Limbs	75	79
	Mainly Involving Upper and Lower Limbs	13	13.6
	Rash Generally Distributed	7	7.4
Associated Clinical Findings		72	75
	Joint Pains and Swelling	54	56.3
	Gastro-intestinal Symptoms	47	48.9
	Abdominal Pain	39	40.6
	Nausea and/or vomiting	4	4.2
	Colitis and Intussusception	1	1
	Evidence of Renal Involvement	35	36.5
	Proteinuria only	19	19.8
	Haematuria only	13	13.5
	Proteinuria, Haematuria and Hypertension	3	3.1

Table 2 Summary of the signs and symptoms noted at first presentation

	Findings at presentation	BP (P95 systolic and diastolic value)	24hr Urine Protein g/day	UAUC mg/g	Serum albumin g/L	eGFR mL/min/ 1.72m^2
Case 1 Male 5yr old	• Palpable purpura over lower limbs and abdomen • Ankle swelling and pain. • No fluid overload	107/85mmHg (BP 108/68)	0.638	6690	24	118
Case 2 Male 10yr old	• Rash involving lower limbs and buttocks • No abdominal pain • No fluid overload	112/72mmHg (BP 115/75)	0.426mg	775	38	158
Case 3 Female 5yr old	• Difficulty walking • Abdominal pain, vomiting • Rash both lower and upper limbs on day 3 • Rash blistered and ulcerated by day 6. • Small amount of free fluid in RIF on ultrasound	128/82mmHg (BP 106/68)	not measured	2.5	44.7	106

One child with nephritic-nephrotic presentation underwent a renal biopsy. The histological findings were consistent with IgA nephropathy.

Two patients experienced serious medical complications. One child developed nephrotic syndrome with heavy proteinuria and hypoalbuminaemia resulting in significant fluid overload with pulmonary oedema. Another patient developed severe abdominal pain and was found to have intussusception, requiring air reduction. Other rare complications such as orchitis, cerebral and cerebellar haemorrhage and pulmonary haemorrhage were not encountered in our study.

Findings on follow-up

93 children (96.9%) were followed-up in clinic at least once; the rest were lost to follow-up. 84 cases (87.5%) showed complete resolution of signs and symptoms within 2 months from presentation and were subsequently discharged by 6 months from the first presentation. Rash recurrence occurred in 12 cases (12.5%), with the majority (75%) of these recurrences occurring within 2 months from the initial presentation with no easily recognisable trigger.

Interestingly, two of the three patients presenting with nephritis and hypertension (Table 2) had a recurrence of HSP and this was

associated with worsening of the kidney disease, as demonstrated in Table 3.

Table 4 and Table 5 represent a summary of the clinical findings that were observed in this study with Table 5 comparing the severity of the rash compared to the renal and extra-renal involvement.

Fisher Exact Test was used to correlate the severity of the rash with the incidence of renal involvement and this revealed a statistically significant association between the two; p=0.008, odds ratio is 0.21 (0.06-0.72) and a relative risk of 0.48 (0.39-0.59) with a severe, ulcerating rash more likely to be associated with nephritis. (Table 5)

Table 3 Clinico-pathological findings during the recurrent episodes of HSP

	Findings during first recurrence	Findings during subsequent recurrences	Kidney biopsy
Case 1 Male 5yr old 2 recurrences	• 5 months from first presentation • Palpable purpura over limbs and trunk, abdominal pain, scrotal swelling • BP 115/70 • Prednisolone 4mg/kg daily for 4 weeks	• 6 m from first presentation • Developed generalised oedema with pulmonary oedema and weight gain of 5.3 Kg • Serum albumin 16.8g/L • UAUC increased to 6690mg/g • Introduced mycophenolate mofetil to high dose oral steroids	IgA nephropathy
Case 2 Male 10yr old 1 recurrence	• 2 months from first presentation • Urine dipstick 4+ protein and 4+ blood • 24 hr urine protein 1.632g/d • BP 110/80mmHg • Started on angiotensin converting enzyme inhibitor (ACEi)	• No further recurrences • Persistent proteinuria. No haematuria • 24hr urine protein 0.6 – 0.7g/d • Receiving ACEi	Not performed
Case 3 Female 5yr old 3 recurrences	• 1 month from first presentation • Serum albumin 35g/L • UAUC 1480-1650mg/g • Hypertensive on ACEi • Introduced furosemide	• Second recurrence 7 months from first presentation, possibly precipitated by a viral URTI • Persistent haematuria 2+ and proteinuria 3+ • UAUC 280-300mg/g • Introduced ACEi • 3rd recurrence 5.5yrs from first presentation • Presented with abdominal pain and purpuric rash involving lower limbs • 24hr urine protein 0.3g/d • BP 120/80mmHg (P90 115/74)	Not performed

Table 4 Summary of clinical manifestations of HSP

HSP rash with involvement of:	number of cases	Fine non-palpable purpura	Palpable Purpura	Ulcerated/ blistering purpuric lesions
No other system	24	23	1	0
Renal system only	4	2	2	0
Renal and musculoskeletal only	16	12	1	3
Renal and gastrointestinal system only	12	11	0	1
Renal, musculoskeletal and gastro-intestinal system	6	3	1	2
Gastro-intestinal involvement only	2	0	1	1
Gastro-intestinal and musculoskeletal system only	27	26	1	0
Musculoskeletal/joints only	5	5	0	0

Table 5 Comparison of the renal and non-renal manifestations against the severity of the purpuric rash.

	Non-renal involvement	Renal involvement
Mild purpura	54	28
Severe Purpura	4	10

In children presenting with proteinuria and/or haematuria there was complete resolution in 47% of cases by 1 year and in 80% of cases by three years. Two cases developed proteinuria during follow-up rather than during the initial presentation with HSP. These occurred within the first four months from presentation and both required a follow-up of over one year for the proteinuria to disappear.

DISCUSSION

This is the first study that characterises the course of HSP in the Maltese paediatric population. The prevalence of HSP is higher in males with a male to female ratio of 1.35:1 which is slightly less than that of 1.8:1 quoted in the literature.[9] The mean age at presentation is similar to that quoted in the literature. The presenting feature of the disease is the ubiquitous rash with a variable

distribution and severity. The majority of the cases (79%) had the typical HSP rash presenting in the lower limbs with only a minority having the upper limbs also affected, or having a generalised rash. Childhood HSP does tend to affect the lower limbs whilst adolescent or adult onset HSP tends to affect mainly the upper extremities more commonly for reasons unknown.[3]

Gastrointestinal involvement, joint involvement and age over 8 years have been shown to be independent risk factors for developing nephritis, increasing the risk 2-3 fold.[3,16] From our study, it is apparent that the severity of the skin rash is significantly associated with the development of nephritis (p=0.008). We also noted that younger children developed a more severe rash than their older counterparts (p=0.02).

HSP associated nephritis (HSN) occurs in about a third of cases and determines the long-term prognosis. At presentation, 36% of cases in our study showed a degree of proteinuria and/or haematuria to suggest HSN and this persisted for at least 1 year of follow-up in half of the cases. A minority (3.1%) had proteinuria, haematuria and hypertension and two cases required immunosuppressive medication and ACE inhibition. The importance of monitoring the urine for proteinuria/haematuria and the blood pressure cannot be overemphasised and recommendations for long-term follow-up have been put forward. HSN tends to develop within the first 4 weeks after the onset of HSP and at most, within the first 3 months.[16]The presence of nephritis at presentation increases the likelihood of developing chronic renal disease.[16] A kidney biopsy may be warranted in selected cases together with consideration of immune suppressive therapy.[11] The use of ACE inhibitors and control of hypertension has been shown to be renoprotective.[12-13] The use of corticosteroids and immunosuppressive therapy is mainly limited to cases with severe nephritis and should be considered after kidney biopsy and consideration of the updated Oxford classification score which is useful in predicting long-term outcomes of HSP nephritis.[13-14]

HSP followed a mild course in the majority of the cases with complete recovery on follow-up. Most of these recoveries occurred in the first 3 months with the rash typically fading within the first 50 days. The recurrence rate was 12.5% and occurred within the first 2 months from the initial presentation but could take up to 5 months. No obvious trigger was identifiable for the recurrence in the majority of cases.

CONCLUSIONS

This study demonstrated that HSP in the Maltese paediatric population has similar presenting and long term clinical characteristics to that of other European populations.[9,10] A limitation of the study was that some mild cases of HSP presentations or relapses may have been treated in the community and would not have been included. Risk factors for developing nephritis are described as an older age at presentation (greater than 8 years), the presence of abdominal pain and recurrence of HSP. We have shown that increasing severity of the purpuric rash at presentation can also increase the likelihood of developing nephritis.

In most cases of HSP, the prognosis for complete remission is good and only a minority develop persistent renal disease requiring specialist management.

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