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Original Research Article

Spectrum of cutaneous manifestations in Wilson's disease in children in a tertiary care center in South India: a prospective study

Karrunya K. J.[1]*, Sumathi Bavanandam[2], Nirmala Dheivamani[2], Vijayabhaskar C. Reddy[1], Manoharan K.[1]

[1]Department of Dermatology, Madras Medical College, Chennai, Tamil Nadu, India
[2]Department of Pediatric Gastroenterology, Institute of Child Health and Hospital for Children, Chennai, Tamil Nadu, India

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***Correspondence:**
Dr. Karrunya K. J.,
E-mail: coolkarru@gmail.com

ABSTRACT

Background: Wilson's disease in children is the most common inherited disorder of copper metabolism in India with varied clinical manifestations secondary to deposition of copper in various organs including skin.
Methods: The aim of the study was to study various cutaneous manifestations of Wilson's disease in south Indian children. A prospective study for a period of one year was conducted at Dermatology and Pediatric Gastroenterology clinic in Government Rajiv Gandhi Hospital, Chennai. Clinical, demographic details, various cutaneous manifestations and results of skin biopsy were analysed.
Results: Out of the total 30 children with Wilson's disease, 93.3% had at least one cutaneous, mucosal, hair or nail findings but not statistically significant between naive and on treatment group. Cutaneous findings, mucosal involvement, hair changes and nail findings were observed in 90%, 36.7%, 46.7% and 60% respectively. Cutaneous findings were more common in liver disease (P value<0.05). Xerosis was the most common cutaneous manifestation seen in 63.3% patients, followed by pigmentation in 36.7% and infection in 30%. KF ring was noted in 53.3%. Icterus and pruritus were seen in one fifth of study children and majority had portal hypertension. Vascular changes like spider nevi, purpura and other features of portal hypertension were noted in 16.6% of study population. Trichomegaly was one of the common hair manifestation found in 9 (30% especially in children already on treatment (p value <0.05). There was no evidence of stainable copper on skin biopsy.
Conclusions: The physicians should be aware of various cutaneous manifestations of Wilson's disease in children.

Keywords: Children, Cutaneous manifestations, Skin biopsy, Wilson's disease

INTRODUCTION

Wilson's disease (WD) is an autosomal recessive, inherited disorder of copper metabolism due to defect in ATP7B gene mutation leading on to defective incorporation of copper into serum ceruloplasmin and its excretion through bile.[1] The ATP7B gene encodes for a P type specific ATPase enzyme which is a cation transport enzyme. This enzyme helps in the transport of copper into the bile thus facilitating its incorporation into the ceruloplasmin.[2] Deposits of copper in various organs including cutaneous tissues occur with varied clinical manifestations. Wilson's disease is diagnosed on the basis of the presence of at least 2 of the following criterias: family history of Wilson's disease, KF ring, low ceruloplasmin levels (<18mg/dL), 24-hour urine copper >100 mg/24-hour, free copper >25 mg/dL and liver copper.[3] Kayser Fleischer (KF) ring and blue lunulae are specific dermatological findings and other cutaneous

findings occur in less than 5% of patients.[4] KF ring is a greenish, gold to brown colored ring formed by the deposition of copper in the Descemet's membrane in the corneal limbus. The disease is classically associated with blue lunulae of the nails (10%), grey brown macular hyperpigmentation and a vague greenish discoloration of the skin. Skin findings are more likely in patients with longer duration of disease. The other cutaneous findings are related to hepatic dysfunction and long-term treatment with penicillamine.[4] The incidence of Wilson's disease is worldwide with a prevalence ranging from 1 in 30,000 to 1 in 100,000.[5] One half of the patients have CNS involvement. There are no current registries in India to determine the incidence, but Taly et al in his study has found that the incidence is more common in India than previously thought.[6] There are very few data on the cutaneous manifestations of Wilsons' disease in Indian children reported in literature and hence the study was undertaken in a tertiary care pediatric center in south India.

METHODS

A prospective observational study for a period of 1 year from September 2013 to August 2014 was conducted at the Department of Dermatology, Rajiv Gandhi Government General Hospital and Pediatric Gastroenterology Department at Institute of Child Health, Chennai. Ethical clearance was obtained to undertake the study. Informed and written consent was taken from the parents. Thirty children aged up to 18 years, of either sex, diagnosed to have WD (hepatic phenotype 22 and neuro phenotype 8) who were willing to participate were recruited and grouped into 2 groups namely Group 1 naïve patients (11) and Group 2 (19) patients on treatment.

Clinical, demographic details and various skin, mucosal, hair and nail changes were recorded in a pre-structured proforma. The skin biopsy was subjected for both H and E and special stain of copper to look for demonstration of copper in the skin and subcutis. A 4-mm punch biopsy was taken from the normal skin of 10 patients and was stained with Eosin and hematoxylin and Copper Rhodanine staining. Skin biopsy tissue was fixed in 10% neutral buffered formalin and embedded in paraffin sections cut at 6 microns and staining was done using 'Rhodanine' method where Rhodanine working solution containing p-Dimethyl aminobenzylinene-rhodanine and Mayer's hematoxylin were used. Eosin and hematoxylin stain was also done. Copper appears as orange/red and tissue elements as light blue on biopsy specimen on staining.

Dermatological examination was categorized under the following categories:

- General examination, nutritional changes, vascular changes, infections, pigmentary changes, mucosal changes, hair changes and nail changes.
- Histopathological examination of skin with special stain for copper.

Statistical analysis was done using SPSS version and expressed in frequency variables.

RESULTS

Majority were in the age group of 6 to 9 years (range 6 years-16 years) with mean age being 10.7±2.9 years. The age of onset of the disease was 8.8 years (range 2-16 years) and the mean duration of the disease was 21.7 months (1 week- 9 years) with male to female ratio of 2:1. Presence of Kayser Fleischer (KF) ring either by naked eye or slit lamp test was seen in 53.3% of total 30 patients (68.7% had hepatic onset of disease and 56.2% were on treatment without any statistical significance between naïve or those on therapy, P value >0.05).

Dermatological manifestations

28 patients (93.3%) had at-least one cutaneous, mucosal, hair or nail findings. 27 patients (90%) had cutaneous findings, 11 patients (36.7%) had mucosal findings, 14 patients (46.7%) had hair findings and 18 patients (60%) had nail findings. 4 patients had all the above findings. The cutaneous findings are listed in Table 1.

Table 1: Various dermatological findings.

Features	No. of children (n)	%
KF ring	16	53.3
Cutaneous	27	90
Mucosa	11	36.7
Hair changes	14	46.7
Trichomegaly	9	64.3
Sparse hair	5	16.7
Nail changes	18	60
Pruritus	6	20
Icterus	6	20
Pigmentation (more in liver disease)	11	36.7
Vascular	5	16.6
Neurosis	21	63.3
Infections (Pityriasis versicolor, wart, molluscum contagiosum, impetigo-2 each, scabies-1)	9	30
Others	16	53.3
Skin copper	Nil	

Xerosis was the most common cutaneous manifestation in 63.3% patients, followed by pigmentation in 36.7% and infection in 30%, Icterus and pruritus were seen in 6 patients (20%) each and were associated with portal hypertension in 5 patients. Cutaneous findings were more

common in hepatic onset disease (P value <0.05) with xerosis, mucosal and nail changes being common.

Xerosis (63.3%) was the most common manifestation in malnourished children with liver disease, 52.6% in naive versus 47.3% on treatment) without any statistical significance.

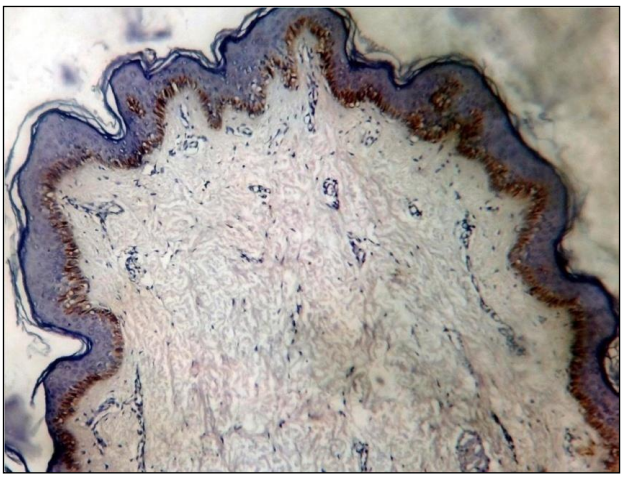

Figure 1: Rhodanine staining of skin showing no copper deposits.

Pigmentary changes in the form hyperpigmentation were observed in 8 patients (26.6%) mainly involving the lower extremities in naive children and all except one had liver disease. Pityriasis alba was observed in 2 malnourished children (6.7%), and acanthosis nigricans in one. The vascular changes consisted of spider nevi and purpura in 2 patients (6.7%) each and palmar erythema in 1 patient, associated with portal hypertension. 30% of children had infections and the common infections encountered were pityrisis versicolor, wart, molluscum contagiosum, impetigo in 2 patients each and scabies in 1 patient. The other cutaneous findings that were found were acne vulgaris in 3 whereas, seborrheic dermatitis, keratosis pilaris over the forearms, atrophic patches over the legs and atopic dermatitis 2 in each. Less common findings were Café au lait macule, urticaria, gynaecothelia, striae, phrynoderma each in 1.

Mucosal involvement was seen in 11 patients (36.7%) who had liver disease with equal distribution between naïve and those on treatment without statistical significance. 6 (20%) children had cheilitis and one third were malnourished. Oral candidiasis was seen in 4 patients and hyperpigmentation of the tongue was seen in 1 patient.

In the present study, hair involvement was seen in 14 patients (46.7%) and trichomegaly was the most common manifestation seen in 9 patients (64.3%) with male:female ratio 2:1 and remaining five had sparse hair, with no statistical difference between hepatic or neurological involvement and naïve or already on treatment group. Nail involvement was seen in 18 (60%) children and half of them had leuconychia followed by clubbing in 5 patients with portal hypertension. Beau's lines were observed in 2 patients. Nail involvement was more with liver disease but with equal distribution between 2 groups. Various dermatological findings are illustrated in Table 1.

Skin biopsy:

Skin was normal on both H and E stain and on Rhodanine staining without any deposits of copper in the dermis or periappendageal areas as shown in Figure 1.

DISCUSSION

Wilson's disease is a rare autosomal recessive disorder of copper metabolism with reported prevalence ranging from 1 in 30,000 to 1 in 100,000.[3] In the present study, the mean duration of the disease was 21.7 months (range 1 week to 9 years) and majority of the patients had the disease for more than 6 months with male female ratio of 2:1. Panagariya A et al, had observed the mean duration to be 25.2 months with male preponderance (67%).[7] Hepatic and CNS involvement were seen in 73.3% and 26.7% respectively similar to Stephania et al study.[8]

Presence of KF ring was seen in 53.3%, more with liver involvement (68.7%). The reported frequency of KF ring in various Indian series have shown to range from 86.6 to 97.1% and study by Gow PJ et al showed that KF rings are present in only 50% to 62% of patients with mainly hepatic disease at the time of diagnosis similar to the present study.[3]

Dermatological manifestations

Copper is mainly deposited in skin fibroblasts and the Wilson protein is expressed in the human skin epithelium. In children, 70% have at least one skin or mucosal finding including xerosis (46%) and white bands on the nails (19%).[9] It is classically associated with blue lunulae of the nails (10%), grey-brown macular hyperpigmentation especially of the lower extremities where it may have a rippled appearance and a vague greenish discoloration of the skin of the face, neck, and genitalia.[9] D-penicillamine which is used for treatment can interfere with collagen cross links leading to the alterations of the collagen and elastin. Other changes include alterations in the reticular dermis proportional to the duration of treatment and consisted of polymorphous aggregates of elastin connected to apparently normal elastin fibers. Lumpy-bumpy elastic fibers are pathognomonic for penicillamine-induced elastosis.[10]

Present study showed 93.3% had at-least one cutaneous, mucosal, hair or nail findings. According to Seyhan M et al, 26 (70.3%) had at least one dermatological finding with 25 (67.6%), 5 (13.5%), 9 (24.3%) patients having skin, mucosal and nail findings, respectively.[9]

Xerosis was the most common manifestation seen in 63.3% patients, followed by pigmentation in 36.7% and infection in 30%. Icterus and pruritus were seen in 6 patients (20%) each and were associated with portal hypertension in 5 patients. The results were thus concordant with Seyhan M et al with the most prevalent cutaneous manifestation being xerosis with a frequency of 45.7% (n = 17) and pruritus observed in 9 patients (24.3%) with portal hypertension.[9]

Pigmentary changes in the form hyperpigmentation was observed in 8 patients (29.6%) mainly involving the lower extremities, pityriasis alba in 2 patients (7.4%), both of whom were malnourished and acanthosis nigricans in 1 patient was observed which was more compared to Seyhan M et al study.[9] The skin hyperpigmentation is due to increased melanin in basal cell layer without alteration of skin structure or increased copper deposition.[11]

The vascular changes were seen in 16.6% patients mainly associated with portal hypertension and in Seyhan M et al study 10.8% patients had vascular changes.[9] The vascular changes occur due to vasodilation from increased prostacyclins and nitric oxide that accumulate in patients with liver disease. It is also associated with increased estrogen and estrogen/androgen ratio.[12]

Xerosis (63.3%) was the most common manifestation especially in malnourished, the probable reasons being chronic course of the disease and copper restricted diet. (52.6% in treated versus 47.3% naïve patients). Turkish study reported the frequency of xerosis in 11.8% of healthy children indicating that the prevalence of Xerosis in children with WD is higher than healthy children.[13] Infections like pityriasis versicolor, wart, molluscum contagiosum, impetigo and scabies were seen in one third of our children though less common similar to Seyhan M et al.[9] Mucosal involvement was seen in 36.7% (cheilitis - 6 patients) and more in malnourished children which was higher than observed Seyhan M et al (10.8%).[9]

Hair involvement was seen in 46.7% and trichomegaly, the excessive growth of eyelashes was the most common manifestation seen in 9 patients (30%) followed by sparse hair. Trichomegaly is not a specific finding of WD as it can occur in congenital syndromes, HIV infections, autoimmune disease and also with drugs like phenytoin, zidovudine, latanoprost, cyclosporine and D-penicillamine.[14] The association of trichomegaly with D-penicillamine needs further studies. Seyhan et al in their study observed trichomegaly in 1 patient (2.7 %).[9]

Nail involvement was seen in two third of our patients with leuconychia in one third of them, followed by clubbing, pitting and Beau's lines, which was more than by Seyhan et al.[9]

In the present study, skin biopsy was done from the normal skin in 10 patients and there were no deposits of reddish brown copper in the dermis or periappendageal areas though copper spill over is known to occur in WD. The skin biopsy done in early stages shows excessive copper deposition in the skin, that is due to the excessive spill over from the liver tissue. Copper is mainly deposited in skin fibroblasts and the Wilson protein is expressed in the human skin epithelium.[15,16]

CONCLUSION

Wilson's disease is a rare disease whose diagnosis can be delayed because of its non-specific early manifestations and the low index of suspicion on the part of the physicians. In children especially, earlier recognition and treatment is important to prevent the progression of this disease, which can be associated with severe morbidity. Thus the physician should be aware of the various cutaneous manifestations of Wilson's disease for the early diagnosis and prompt treatment of the disease.

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