Waardenburg syndrome-associated focal segmental glomerulosclerosis: A rare presentation

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ABSTRACT

Waardenburg syndrome (WS) is characterized by auditory and pigmentary disorders with an incidence of 1:40,000. Renal involvement is rare in WS. A 10-year-old male, diagnosed as nephrotic syndrome at 4 years, was presented in relapse. A renal biopsy performed at 6 years revealed evidence of focal segmental glomerulosclerosis. The child had morphological findings which were suggestive of WS. Hence, a diagnosis of WS type 1, with frequently relapsing nephrotic syndrome, was made. The possible genetic basis of renal involvement in WS needs to be evaluated.

Key words: *Focal segmental glomerulosclerosis, Nephrotic syndrome, Waardenburg syndrome*

Waardenburg syndrome (WS) is a rare genetic syndrome characterized by varying degree of auditory and pigmentary disorders. Its incidence is approximately 1 in 40,000 [1]. Focal segmental glomerulosclerosis (FSGS) is an important cause of non-minimal nephrotic syndrome in children [2]. Nephrotic syndrome with minimal change disease has been reported with WS [3]; however, in this case, the biopsy showed FSGS. Here, we present a case of type I WS with nephrotic syndrome due to FSGS.

CASE REPORT

A 10-year-old male, known case of WS type I, with frequently relapsing nephrotic syndrome, was presented with complaints of swelling over body for 1 month and decreased urine output for 1 week. The child was diagnosed as a case of nephrotic syndrome at the age of 4 years. A renal biopsy performed at 6 years of age showed evidence of FSGS. The child was deaf and mute since birth and had bright blue iris. He was born out of a non-consanguineous marriage and had a history of similar blue eyes in paternal grand uncle, but there was no family history of hearing inability/premature greying of hair or renal diseases. There was no other significant history/personal history/family history. The development of the child was normal in all fields except language field. On general examination, he had a pulse rate of 90/min, respiratory rate of 20/min, and blood pressure of 104/72 mm Hg. There was no pallor/icterus/cyanosis/clubbing, but bilateral pitting pedal edema was present. He was anthropometrically normal for age.

On head to toe examination, he had peculiar findings: He had medial eyebrow flare, epicanthus inversus, telecanthus, broad nasal bridge, and smooth philtrum. His hair and skin were normal, and there were no pigmentary anomalies of hair/skin. A detailed ocular and otologic examination was carried out and his visual acuity and color vision were normal, but he had bilateral hypochromic iridis with bilateral diffuse choroidal hypopigmentation. On ocular measurements, the intercanthal distance was 41 mm, outer canthal distance was 83 mm, and interpupillary distance was 52 mm. The calculated W index from these parameters was 2.767 (Fig. 1). A value of >1.95 is suggestive of dystopia canthorum which, in this case, suggested WS type I. On audiometry, he had bilateral profound sensorineural hearing loss. On abdominal examination, the only positive finding was shifting dullness. Respiratory system, cardiovascular system, and central nervous system were normal on examination.

Laboratory investigations were also performed and his complete blood count and liver function tests were within normal limits, but he had hypoproteinemia, hypoalbuminemia, and deranged lipid profile. His protein level was 4.8 g/dL, albumin was 1.8 g/dL, total cholesterol levels were 691 mg/dL, triglyceride levels were 531 mg/dL, and low-density lipoprotein levels were 576 mg/dL. His serum viral markers were nonreactive, and his blood and urine culture reports were sterile.

Kidney biopsy sample, on direct microscopy, revealed six glomeruli of which two were slightly enlarged in size along with mild mesangial expansion and neutrophilic infiltration. Two glomeruli showed the segmental collapse of capillaries with sclerosis and synechiae formation, whereas the overlying podocytes showed marked vacuolation. Tubules showed marked degenerative changes with resorption droplets, drop out necrosis, and mitosis; occasional areas of tubular atrophy were also noted. Interstitium showed focal areas of fibrosis. Direct

Table 1: Subtypes of WS and genes involved

Type	Gene involved	Inheritance	Special feature
Type I	PAX3	AD	Dystopia canthorum
Type II	MITF, WS2, and SNAI2	AR	Hearing loss and iris hypopigmentation are more common
TYPE III	PAX3	AD	Type I plus limb deformity
TYPE IV	EDNRB, EDN3, and SOX10	AR	Hirschsprung disease

WS2: Waardenburg syndrome2, PAX 3: Paired box 3 transcription factor; MITF: Microphthalmia-associated transcription factor; EDN 3: Endothelin 3; EDNRB: Endothelin receptor type B, SNAI2: Snail homolog 2; SOX 10: Sry box 10 transcription factor; AD: Autosomal dominant; AR: Autosomal recessive

Figure 1: Child with Waardenburg syndrome showing dystopia canthorum, synophrys, blue iris, and broad nasal bridge

immunofluorescence of the biopsy sample showed immunoglobin (IgG) 1+, IgA negative, IgM 2+, and C3 levels of 1+ to 2+. These features were suggestive of FSGS with superadded tubular necrosis. The physical findings of this child were suggestive of WS type I. Genetic testing and electron microscopy could not be done in our case due to non-availability. This child responded well to prednisolone treatment and is in remission until date.

DISCUSSION

Waardenburg syndrome is a rare genetic syndrome with an estimated incidence of 1 in 40,000 people [1]. It accounts for 2–5% of cases of congenital hearing loss, and it is the most common autosomal dominant cause of congenital hearing loss [4]. It is classified into four types based on clinical features and genetics [Table 1].

The genes involved in WS play an important role in the development of eye, ear, and melanocytes. WS types I and III are inherited as autosomal dominant pattern, but *de novo* mutations also occur when an affected individual does not have an affected parent. In this case, it seems to be a *de novo* mutation as the child does not have an affected parent. WS type I is diagnosed if there are two major criteria or one major plus two minor criteria [5].

Major Criteria

The major criteria are as follows:

1. Congenital sensorineural hearing loss,
2. White forelock or hair hypopigmentation,
3. Pigmentation abnormality of the iris such as complete heterochromia iridum (irides of different color), partial/segmental heterochromia (two different colors in the same iris, typically brown and blue), or hypoplastic blue irides or brilliant blue irides,
4. Dystopia canthorum, W index >1.95, and
5. Affected first-degree relative.

Minor Criteria

The minor criteria are as follows:

1. Skin hypopigmentation (congenital leukoderma),
2. Synophrys and/or medial eyebrow flare,
3. Broad/high nasal root, low-hanging columella,
4. Underdeveloped alae nasi,
5. Premature gray hair (age <30 years).

WS types I and II have almost same clinical presentation. The distinction among the two is made on the basis of W index. W index >1.95 is suggestive of type I and W index <1.95 is suggestive of type II. In this case report, the child had three major criteria (congenital sensorineural hearing loss, pigmentary abnormality of iris, and W index >1.95) and one minor criteria (broad nasal bridge). Hence, he was considered as a case of WS type I.

FSGS occurs in about 30–35% of children with non-minimal nephrotic syndrome. It can be either idiopathic or secondary to certain conditions. Several genes have been implicated in the development of FSGS: Podocin, alpha-actinin-4, transient receptor potential cation channel subfamily C member 6 protein, inverted formin-2, myosin heavy chain-9, and paired box 2 transcription factor (PAX 2). It is characterized by proteinuria, edema, hypoalbuminemia, and hyperlipidemia. FSGS is most commonly present as nephrotic syndrome (90%), hematuria (60–80%), asymptomatic proteinuria (10%), and hypertension (20%). In children, it can present as initial or late steroid resistance.

Renal involvement in a case of WS is rare, wherein only a few cases have been documented in literature. In 1997, Jenkaukiene reported a case of 16-day-old girl child with WS type I with the right multicystic dysplastic kidney and hydronephrosis in the left kidney [6]. In 2005, Saniye reported a case of 12-month-old girl with WS type I with double collecting system of the left kidney and ureteropelvic junction obstruction of the right kidney. In addition, they suggested that urologic evaluation in patients with WS to avoid life-threatening complications [7]. Avesh *et al.* reported a case of 19-year-old female with type II WS with minimal change nephrotic syndrome. In this case, the authors suggested the need for further genetic studies for evaluation of the association between nephrotic syndrome and WS [3]. In our case, FSGS was a cause of nephrotic syndrome in a young boy with WS type I with *de novo* mutation. The management of children with WS consists of proper audiologic evaluation and appropriate hearing aids and genetic counseling. Genetic testing consists of identifying the pathogenic PAX 3 mutation.

CONCLUSION

Since renal involvement in WS is being reported, it is suggested that evaluation of renal system must be considered. The genetic association of WS with nephrotic syndrome needs further evaluation.

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