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Late diagnosed Ochoa Syndrome: Case report and literature review

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Abstract

Ochoa syndrome, also known as urofacial syndrome, is a rare genetic disease (OMIM #236730) with autosomal recessive inheritance of mutations in the heparanase 2 (HPSE2) and the LRIG2 genes, characterized by functional obstructive uropathy and unusual facial abnormalities. Progression to renal failure if not early diagnosed is inevitable. The therapeutic goals are to restore bladder emptying, preventing damage to the urinary tract with the use of prophylactic antibiotics, clean intermittent catheterization, anticholinergic use, botulinum toxin injection, urinary diversion and bladder augmentation to slow the evolution of the disease. This article aims to report a patient with late diagnosis of Ochoa Syndrome, as well as describe its characteristics and clinical outcome.

Keywords

Ochoa Syndrome; urofacial syndrome; nonneurogenic neurogenic bladder; HPSE2; LRIG2.

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Introduction

Ochoa syndrome, also known as urofacial syndrome, is a rare condition characterized by functional obstructive uropathy and unusual facial abnormalities. It progresses to renal failure if not diagnosed early. The syndrome with mutations in the heparanase 2 (HPSE2) and the LRIG2 genes has an autosomal recessive inheritance pattern which means, both sexes are equally affected and with an increased incidence when parents are consanguineous [1,2].

First observed in the 60's by Dr. Bernardo Ochoa, it was described in the literature only in 1979 by Dr. Rafael Elejalde, who defined it as Ochoa Syndrome and started the investigation to find the cause [2].

The syndrome is a subset of nonneurogenic neurogenic bladder first described by Hinman, and the explanation for the inverted expression would be the proximity of the micturition center with laughter and crying, that are located in the upper bridge of the midbrain, where even a subtle neurological injury could simultaneously affect both regions [3].

This article aims to report a patient with late diagnosis of Ochoa Syndrome, as well as describe its characteristics and clinical outcome.

Case Reports

A 7 year old boy referred to our clinic with chronic renal failure for 6 years. Creatinine clearance was about 23 ml/min. Complaint of several episodes of urinary infection and bedwetting. He was in long-term use of oxybutynin and doxazosin. His parents were not related and he had two brothers, of which one died from gastroschisis complications when 1 year and 3 months old. There was no other history of renal failure in the family. Ultrasound examination showed important bilateral hydronephrosis and high post-void residual urine volume with thickened bladder walls [Fig. 1A,B].

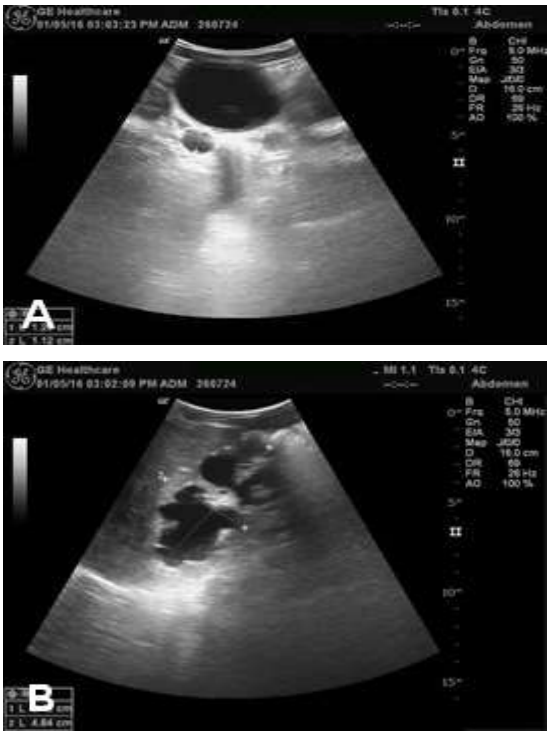
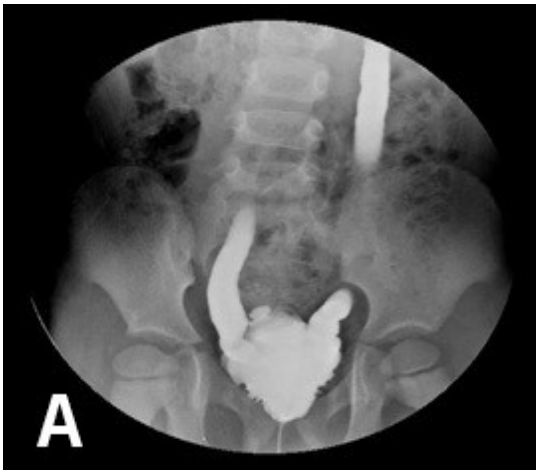


Fig. 1. (A,B) Ultrasound with bilateral hydronephrosis.

Cystography demonstrated vesicoureteral reflux grade V with bladder trabeculation and thickening [Fig. 2A,B].



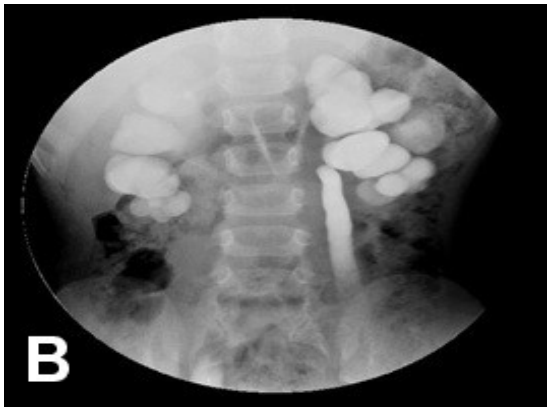


Fig. 2. (A,B) Cystography demonstrating vesicoureteral reflux grade V with bladder irregularity and wall thickening.

Urodynamic study showed bladder cystometric capacity of 212 ml with 38 water centimeters pressure, bladder compliance of 5.5 ml/water cm, absence of uninhibited contractions of the detrusor with flowmetry revealing hesitant and interrupted pattern with urinated volume of 150 ml and 62 ml post void residual urine, with a peak flow of 3.7 ml / second and detrusor pressure at the opening of 76 centimeters of water [Fig. 3 and 4].

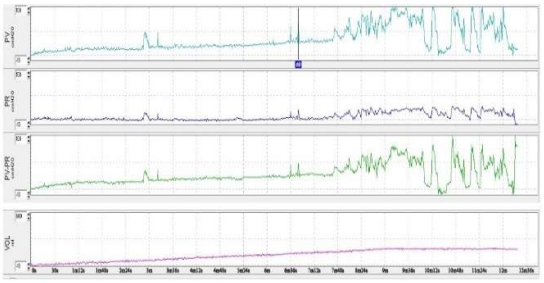


Fig. 3. Urodynamic study showed bladder cystometric capacity of 212 ml with low compliance.

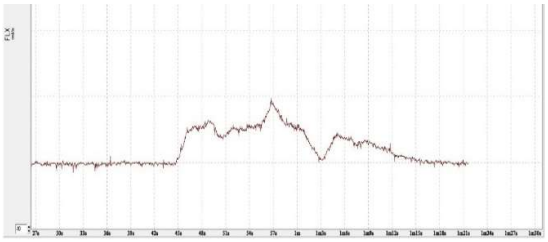


Fig. 4. Flowmetry revealing hesitant and interrupted pattern with urinated volume of 150 ml and 62 ml post void residual urine.

The cystoscopy excluded posterior urethral valve. The clinical evaluation clearly presented facies with inverted smile [Fig. 5].

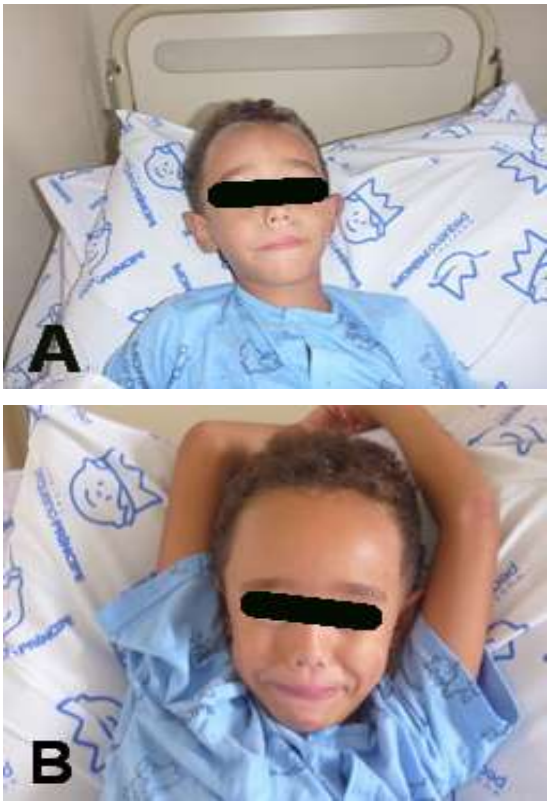


Fig. 5. (A,B) Inverted Smile – on the picture A; it is possible to observe the patient with the face relaxed while the picture B demonstrates the patient smiling.

Due to failure of clinical treatment, elevated post-micturition residue and recurrent episodes of urinary tract infection, a continent conduit for bladder emptying - Mitrofanoff with appendix was indicated and performed by laparoscopy. New cystoscopy was conducted with botox application – 166 units – in a straight line across the bladder wall except for the trigone region in order to improve bladder capacity. During follow-up renal function improved. Serum creatinine lowered to 1 mg/dl, and creatinine clearance improved to 42ml/min, with normal blood pressure with the patient performing clean intermittent catheterization every 4 hours.

Discussion

The mechanisms of Ochoa syndrome are not well understood. This syndrome is considered to represent a subgroup of the non-neurogenic bladder dysfunction, characterized by non-neuropathic bladder-sphincter dysfunction, along with a characteristic inversion of the facial expression with laughing [3].

Rondon et al retrospectively reported six cases. Physical examination revealed in all evaluated patients peculiar facial expression and abnormalities of the facial muscles in an attempt to smile [4].

Akl and Momany, through a case report showed not only the characteristic facial expression, as well as the heritage of micturition disorders and malformations of the urinary tract [1].

In a study with three patients, Nicanor et al reported that all of the cases initially presented acute renal failure, urinary tract and severe dysfunction of elimination [5].

According to Woolf et al, the main prenatal characteristics were increased bladder and ureterohydronephrosis. After birth 30% of patients had severe constipation and in radiological evaluation showed incomplete emptying of the bladder after voiding in the ultrasonography, absence of lesions in urethral lumen in cystoscopy. Cystometry showed high intravesical pressures with dysynergia and, bladder with low capacity and trabeculated walls in cystography [6].

Recent researches were found the defective gene for urofacial syndrome in a region on chromosome 10q23-q24, with evidence of mutations on Heparanase 2 (HPSE2) gene that would be responsible for Ochoa syndrome. Bulum et al found a mutation in HPSE2 gene in a patient with family urofacial syndrome, after analyzing seven patients from five different families [7].

Roberts et al demonstrated in vivo that heparanase-2 is necessary for functional peripheral neural development and also modulates growth factor signaling during embryogenesis. These factors therefore

would support the claim that the urofacial syndrome has its key feature being a congenital peripheral neuropathy [8].

Daly et al showed that mutations on HPSE2 represses the activity of heparanase 2, causing urofacial syndrome in families of different ethnicities. They showed that this gene is associated with the facial expression, urination and also control the bladder smooth muscle and function involving the morphology of the renal tract [9].

According to a study by Pang et al, which identified three loss of function mutations in the HPSE2 gene in patients with urofacial syndrome in different countries, it is clear that this gene would be a major contributor to the syndrome [10].

Stuart et al studied and showed that the LRIG2 and HPSE2 genes are needed so that there is innervation and normal lower urinary tract neural function. Mutations in these two genes would result in a specific phenotype of urofacial syndrome [11].

Several case reports also showed inbreeding of the parents of patients with Ochoa syndrome. Rondon et al reported a case of a patient whose parents were cousins [4]. Nicanor et al described a case of a patient whose parents reported that two aunts had similar smile findings but no urinary retention at any time [5]. Here we can assume about other genetic mutations and mechanisms involved in the formation of the syndrome which should be studied further. Two reported cases did not have a family history of Ochoa syndrome. In a case reported by Akl and Momany, there was a positive family history of the facial grimace without mention of any overt urological anomaly [1].

The therapeutic goals are to restore bladder emptying and prevent urinary tract injury. The use of prophylactic antibiotics, clean intermittent catheterization, anticholinergic, botulinum toxin injection, urinary diversion and bladder augmentation are an attempt to slow the evolution of the patients to chronic renal failure requiring kidney transplantation [6].

The case presented here showed a patient that was late referred to our service, with already installed renal failure and without previous clinical or genetic diagnosis of Ochoa Syndrome. So far measures to delay dialysis and kidney transplantation indication were performed.

Conclusion

Early recognition of this rare syndrome is essential to the restoration of balanced bladder emptying and the prevention of upper urinary tract deterioration. An aggressive urological management can be necessary to improve bladder emptying and

avoid infections. Physicians should be aware of this syndrome when the combination of urological problems and inverted facial expression upon attempts to smile is observed. Carrier testing for at-risk relatives and prenatal testing of pregnancies at increased risk can be performed if the pathogenic variants in the family are known [12].

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References

1. Akl KF, Al Momany HM. Urofacial syndrome. Saudi J Kidney Dis Transpl. 2012 ;23(2):346-8.

2. Tu Y, Yang P, Yang J, et al. Clinical and genetic characteristics for the Urofacial Syndrome (UFS). Int J Clin Exp Pathol. 2014;7(5):1842-8.

3. Stamatiou K, Tyritzis S, Karakos C, Skolarikos A. Urofacial syndrome: a subset of neurogenic bladder dysfunction syndromes? Urology. 2011;78(4):911-3.

4. Rondon AV, Leslie B, Netto JM, et al. The Ochoa urofacial syndrome: recognize the peculiar smile and avoid severe urological and renal complications. Einstein (Sao Paulo). 2015;13(2):279-82.

5. Nicanor FA, Cook A, Pippi-Salle JL. Early diagnosis of the urofacial syndrome is essential to prevent irreversible renal failure. Int Braz J Urol. 2005;31(5):477-81.

6. Woolf AS, Stuart HM, Roberts NA, McKenzie EA, Hilton EN, Newman WG. Urofacial syndrome: a genetic and congenital disease of aberrant urinary bladder innervation. Pediatr Nephrol. 2014;29(4):513-8.

7. Bulum B, Özçakar ZB, Duman D, et al. HPSE2 mutations in urofacial syndrome, non-neurogenic neurogenic bladder and lower urinary tract dysfunction. Nephron. 2015;130(1):54-8.

8. Roberts NA, Woolf AS, Stuart HM, et al. Heparanase 2, mutated in urofacial syndrome, mediates peripheral neural development in Xenopus. Hum Mol Genet. 2014;23(16):4302-14.

9. Daly SB, Urquhart JE, Hilton E, et al. Mutations in HPSE2 cause urofacial syndrome. Am J Med Genet. 86(6):963-9, 2010.

10. Pang J, Zhang S, Yang P, et al. Loss-of-function mutations in HPSE2 cause the autosomal recessive urofacial syndrome. Am J Hum Genet. 2010;86(6):957-62.

11. Stuart HM, Roberts NA, Burgu B, et al. LRIG2 mutations cause urofacial

syndrome. Am J Hum Genet. 2013;92(2):259-64.

12. Newman WG, Woolf AS, Stuart HM. Urofacial Syndrome. 2013 Aug 22. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Fong CT, Mefford HC, Smith RJH, Stephens K, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016.

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