Case Report

Neurogenic bladder as a lurking complication in Moebius syndrome

Yuichiro Tanaka a,⇑, Takanobu Maekawa a, Rumiko Eura c, Yuichi Hasegawa b, Mitsuru Kubota a

a Department of General Pediatrics and Interdisciplinary Medicine, National Center for Child Health and Development, Tokyo, Japan
b Division of Pediatric Urology, National Center for Child Health and Development, Tokyo, Japan
c Department of Urology, Kagoshima University, Kagoshima, Japan

Received 28 January 2021; received in revised form 7 July 2021; accepted 15 July 2021

Abstract

Moebius syndrome (MBS) is a congenital disorder characterized by facial and abducens palsy, sometimes accompanied with other cranial nerve palsies and comorbid conditions. Anatomical anomalies of the brainstem are assumed to be major etiologies of MBS. Its phenotypic presentation can be variable. We report a female patient with MBS who presented with neurogenic bladder (NB). She was born via normal vaginal delivery. At birth, she showed bilateral abducens palsy and right facial palsy. We diagnosed MBS by cranial computed tomography scan and magnetic resonance imaging. She had recurrent urinary tract infection. Hydronephrosis was noted on ultrasonography and bilateral vesicoureteral reflux (grade 5) on voiding cystourethrography. Urodynamic investigation showed detrusor overactivity and detrusor-sphincter dyssynergia, which follow the pattern of NB resulting from infrapontine-suprasacral lesions. Patients with MBS have lower brainstem dysfunction, and accordingly we should be aware of NB.

Keywords: Moebius syndrome; Pons; Neurogenic bladder

1. Introduction

Moebius syndrome (MBS) (MIM 157900) is a rare (the prevalence is estimated to be 0.002% of births) congenital cranial dysinnervation disorder characterized by non-progressive, symmetrical or asymmetrical facial palsy and impairment of ocular abduction, due to paralysis or weakness of the facial (CN VII) and abducens (CN VI) nerves, and frequently other cranial nerves [1,2]. The broad spectrum of neuropathological and neuroradiological findings suggests that MBS is due to rhombencephalic maldevelopment [1]. Both intrauterine environmental and genetic factors have been proposed for the etiology and pathogenesis of MBS. A disruption of blood vessel migration during embryologic development, which can be secondary to misoprostol or cocaine exposure during pregnancy, has been hypothesized to cause hindbrain hypoxia, resulting in cranial nerve dysfunction [3–5]. Patients with MBS have lower brainstem dysfunction and comorbid conditions which sometimes render them technology-dependent [6–9]. The brainstem, particularly the pons, plays an important role in the neurological control of lower urinary tract (LUT) function, and therefore, diseases which involve the brainstem sometimes cause neurogenic bladder (NB) [10–12].

We report a female case of MBS. She had an exceedingly severe phenotype and had NB, which is a very rare complication of MBS.
2. Case report

A female neonate was born at 39 weeks gestation via normal vaginal delivery. All prenatal serology results were negative. Birth weight was 2122 g, and Apgar scores were 8 and 9, at 1 and 5 min, respectively. After birth, the physical examination revealed bilateral abducens palsy and an expressionless face with defect of lateral gaze, a right lagophthalmos, and a small mouth with downturned right corner which manifested right facial palsy. Restricted mouth opening was so severe that she could open her mouth only 5 mm. She also showed dysphagia. Cranial MRI showed hypoplasia of bilateral abducens and right facial nerves and a right dominant hypoplasia of the brainstem, mainly the pons (Fig. 1A–C). Cranial CT revealed symmetrical punctate calcifications, not only in the dorsal portions of the midbrain, pons, and medulla, but also in the wall of the third ventricle (Fig. 2). The results of laboratory tests for congenital infectious diseases, including cytomegalovirus, rubella, and *Toxoplasma*, were negative, and G-bandning chromosome analyses showed a normal karyotype (46, XX). These findings confirmed the diagnosis as MBS. Even though no anomaly of the kidney and urinary tract were detected on fetal ultrasonography, she had urinary retention since shortly after her life and recurrent urinary tract infection; we performed investigations for the kidney and urinary tract when she was two months of age. Ultrasonography and voiding cystourethrography revealed bladder wall irregularity, hydronephrosis, bilateral grade 5 vesicoureteral reflux, and urinary retention (Fig. S1). No anomaly of the spinal cord was detected on MRI. We administered antimicrobial prophylaxis and indwelling balloon catheter. Because her parents could not perform clean intermittent catheterization, we changed balloon catheter in outpatient. When she was two years of age, we performed a urodynamic investigation that showed detrusor overactivity and detrusor-sphincter dyssynergia (Fig. 3). Because parents became able to do clean intermittent catheterization, we therefore administered anticholinergic medication and changed from indwelling balloon catheter to clean intermittent catheterization instead of vesicocutaneostomy considering their values.

3. Discussion

We presented an exceedingly severe case of MBS. Furthermore, this case presented NB as a very rare complication of MBS even though MBS often shows anatomical abnormalities and dysfunctions of the brainstem [6–9,13,14].

Previous studies showed that MBS can be associated with other cranial nerve palsies, and absent blink reflex, jaw ankylosis, absent gag reflex, and tongue atrophy were frequently observed. Global developmental delay can be variable and not common in MBS, and some patients required specific therapies included medical home care [6–8,13,14]. Our case showed not only typical comorbid conditions of MBS but also extremely severe global developmental delay and needed several medical home care (Table S1).
NB is a broadly used term to denote LUT dysfunction as a sequela of neurological disease. NB consists of problems with capacity, retention, or voiding. The pattern of bladder dysfunction following neurologic disease depends on the site of the lesion along the neurological axis. The reflex activation of the urinary bladder is regulated by the pontine micturition center or Barrington’s nucleus (BN). The BN is located in the dorsal part of the caudal pontine tegmentum next to the periaqueductal gray matter (PAG), ventral to the aqueduct, and rostro-ventro-medial to the locus coeruleus. In the sacral spinal cord there is a group of neurons that receives information on bladder filling and sends excitatory ascending fibers to the PAG exciting the BN and initiating the micturition reflex through the activation of the detrusor muscle [11]. The problem with the storage function of the bladder is caused by suprapontine or infrapontine lesions and lesions above the sacral spinal cord resulting in detrusor overactivity [12,15]. The problem with voiding is caused by infrapontine lesions resulting in detrusor-sphincter dyssynergia. For example, urofacial syndrome, which is characterized by urinary bladder voiding dysfunction and abnormal facial movement with expression, shows detrusor overactivity and detrusor-sphincter dyssynergia, but does not show some central nervous system palsies, as in our case [16,17]. On the other hand, patients with acute brainstem stroke and Wernicke’s encephalopathy show not only detrusor overactivity, but also detrusor-sphincter dyssynergia [18,19].

In our case, the pons was hypoplastic from the right ventral side to dorsal and there were calcifications in the brainstem. This may have caused NB that follows the pattern of neurologic disease in infrapontine-suprasacral lesions.

4. Conclusion

Abnormality of the brainstem is frequently observed in MBS, and we should therefore pay attention to LUT dysfunction with MBS.

5. Contributors’ statement page

Drs Tanaka and Maekawa took care of the patient, conceptualized and designed the case report, drafted the initial manuscript, and reviewed and revised the manuscript.

Drs Eura and Hasegawa carried out urologic investigations, conceptualized and designed the case report, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr Kubota conceptualized and designed the case report, drafted the initial manuscript, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank Dr. Yasuyuki Fukuhara from the Division of Medical Genetics, National Center for Child Health and Development for physical examination for diagnosis, Dr. Osamu Miyazaki from the Division of Radiology, National Center for Child Health and Development for voiding cystourethrography, and the medical editor from the Division of Education for...
Clinical Research at the National Center for Child Health and Development for editing this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2021.07.006.

References

[1] Verzijl HT, van der Zwaag B, Cruysberg JR, Padberg GW. Mobius syndrome redefined: a syndrome of rhombencephalic maldevelopment. Neurology 2003;61:327–33.
[2] MacKinnon S, Oystreck DT, Andrews C, Chan WM, Hunter DG, Engle EC. Diagnostic distinctions and genetic analysis of patients diagnosed with moebius syndrome. Ophthalmology 2014;121:1461–8.
[3] Bavinck JN, Weaver DD. Subclavian artery supply disruption sequence: hypothesis of a vascular etiology for Poland, Klippel-Feil, and Mobius anomalies. Am J Med Genet 1986;23:903–18.
[4] Marques-Dias MJ, Gonzalez CH, Rosemberg S. Mobius sequence in children exposed in utero to misoprostol: neuropathological study of three cases. Birth Defects Res A Clin Mol Teratol 2003;67:1002–7.
[5] Puvabanditsin S, Garrow E, Augustin G, Titapiwatanakul R, Kuniyoshi K, Poland-Mobius syndrome and cocaine abuse: a relook at vascular etiology. Pediatr Neurol 2005;32:285–7.
[6] Matsui K, Kataoka A, Yamamoto A, Tanoue K, Kurosawa K, Shibasaki J, et al. Clinical characteristics and outcomes of Mobius syndrome in a children’s hospital. Pediatr Neurol 2014;51:781–9.
[7] Picciolini O, Porrino M, Cattaneo E, Castelletti S, Masera G, Mosca F, et al. Mobius syndrome: clinical features, diagnosis, management and early intervention. Ital J Pediatr 2016;42:56.
[8] Bell C, Nevitt S, McKay VH, Fattah AY. Will the real Mobius syndrome please stand up? A systematic review of the literature and statistical cluster analysis of clinical features. Am J Med Genet A 2019;179:257–65.
[9] Herrera DA, Ruge NO, Florez MM, Vargas SA, Ochoa-Escudero M, Castillo M. Neuroimaging findings in Mobius sequence. AJNR Am J Neuroradiol 2019;40:862–5.
[10] Sakakibara R, Tateno F, Kishi M, Tsuyusaki Y, Uchiyama T, Yamamoto T. [Neurology and the bladder: how to assess and manage neurogenic bladder dysfunction, with particular references to the neural control of micturition]. Brain Nerve 2014;66:527–37. Japanese.
[11] Blanco L, Ros CM, Tarragon E, Fernández-Villalba E, Herrero MT. Functional role of Barrington’s nucleus in the micturition reflex: relevance in the surgical treatment of Parkinson’s disease. Neuroscience 2014;266:150–61.
[12] Panicker JN, Fowler CJ, Kessler TM. Lower urinary tract dysfunction in the neurological patient: clinical assessment and management. Lancet Neurol 2015;14:720–32.
[13] Baraitser M. Genetics of Mobius syndrome. J Med Genet 1977;14:415–7.
[14] McKay VH, Touil LL, Jenkins D, Fattah AY. Managing the child with a diagnosis of Mobius syndrome: more than meets the eye. Arch Dis Child 2016;101:843–6.
[15] Batla A, Parees I, Edwards MJ, Stamelou M, Bhatia KP, Panicker JN. Lower urinary tract dysfunction in patients with functional movement disorders. J Neurol Sci 2016;361:192–4.
[16] Newman WG, Woolf AS. Urofacial Syndrome. 2013 Aug 22 [updated 2018 Jun 7]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2021.
[17] Roberts NA, Hilton EN, Lopes FM, Singh S, Randles MJ, Gardiner NJ, et al. Lrig2 and Hpse2, mutated in urofacial syndrome, pattern nerves in the urinary bladder. Kidney Int 2019;95:1138–52.
[18] Sakakibara R, Hattori T, Yasuda K, Yamanishi T. Micturitional disturbance and the pontine tegmental lesion: urodynamical and MRI analyses of vascular cases. J Neurol Sci 1996;141:103–10.
[19] Yaguchi M, Yaguchi H, Nagaura C. [A case of Wernicke’s encephalopathy with detrusor-sphincter dyssynergia]. Brain Nerve 2015;67:317–21. Japanese.