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Case Report

Mowat-Wilson Syndrome with Nonsense Mutation of ZEB2 Gene: Case Report and Review of the Literature

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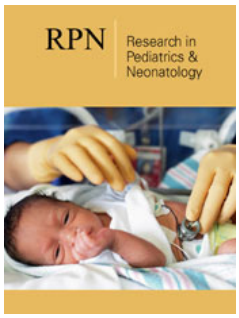

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Introduction

Mowat-Wilson syndrome (MWS) is characterized by distinctive facial appearance in association with multiple congenital anomalies [1-5]. MWS is caused by heterozygous mutations or deletions in the zinc finger E-box-binding homeobox 2 gene, ZEB2 (2q22.3) [5,6]. To date, over 100 deletions/mutations have been reported in patients with a typical phenotype [6]. Prevalence is estimated at 1/50,000 to 1/70,000 live births [5]. To our knowledge, this is the first case of MWS in Taiwan fond to be in association with tracheal stenosis without the presence of pulmonary artery sling and which have not been reported in the previous case reviews.

Case Report

The case is a term male neonate with normal birth weight 2955g born to a healthy mother after an uncomplicated pregnancy. Thirty hours after delivery, he suffered from severe abdominal distention and minimal meconium passage. The diagnosis was later confirmed as Hirschsprung's disease (HSCR) with transitional zone at the sigmoid-descending colon junction by rectal mucosal suction biopsy showing hypertrophied nerve fibers without calretinin-positive nerve fibers. The neonate also showed dysmorphic facial features as described in the attached figure legend. Brain sonography revealed dysgenesis of corpus callosum, which was later confirmed by brain MRI. Bronchoscopy was indicated for difficult intubation procedures and tracheal stenosis with complete tracheal rings was found. Chest computed tomography also revealed mild segmental stenosis at the middle trachea without remarkable cardiovascular anomalies. The baby had clinical seizures with focal epileptic discharges in electroencephalography since around 3 months of age, and he remained seizure-free under anti-epileptic drug monotherapy. Later, genetic survey by Next-Generation Sequencing proved that there was a heterozygous NM_014795: c.2083C>T (p.Arg695Ter) variant in ZEB2 gene. According to ACMG interpretation criteria, this variant is classified as pathogenic (PVS1, PS1, PM1, PM2, PP4) (Figure 1).

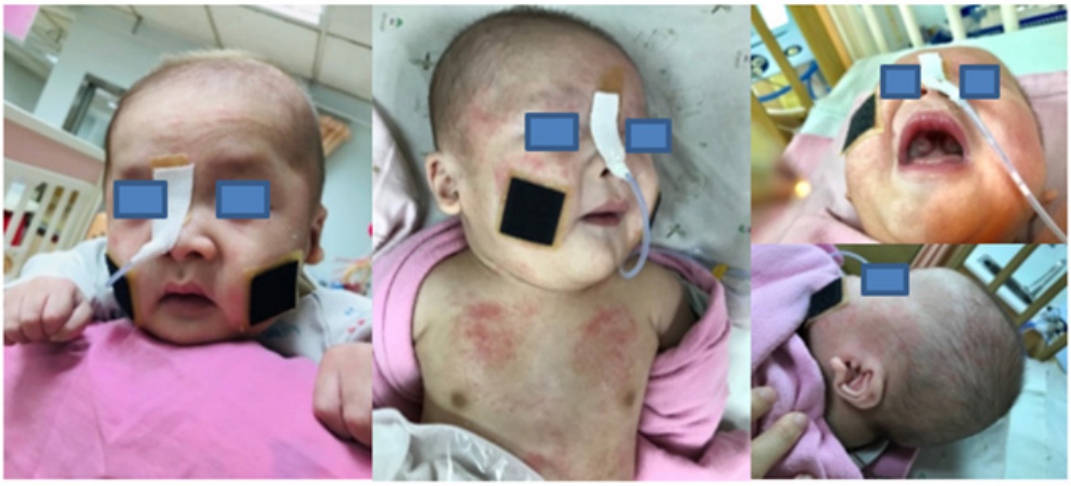

Figure 1: It shows some distinctive facial features found in MWS: square-shaped face with high forehead, frontal bossing, hypertelorism, deep set but large eyes, broad nasal bridge, saddle nose with prominent rounded nasal tip and columella, open mouth with M-shaped upper lip, and uplifted earlobes.

Discussion

Observation of syndromic HSCR was the initial clue for the final diagnosis of MWS in this case. About half of the cases with MWS (44%-57%) were associated with HSCR according to the literature reviews [5,6]. However, HSCR is not present in every infant with MWS and therefore is not a required diagnostic criterion.

Facial dysmorphism may become evident during childhood. Characteristic features include uplifted earlobes with a central depression and large, medially sparse and flaring eyebrows [1,6]. Other non-specific facial features include square-shaped face with high forehead, epicanthal folds, hypertelorism, telecanthus, large deep-set eyes, strabismus, broad nasal bridge, rounded nasal tip, prominent columella, open mouth with M-shaped upper lip, and prominent but narrow and triangular pointed chin with excess nuchal skin and puffy anterior neck [1,6]. Our patient also showed characteristic uplifted earlobes in addition to some of other non-specific features during infancy, but medially flaring eyebrows were not prominent.

Congenital heart defects and urogenital anomalies were noted in about half of the MWS cases, 52% and 51% respectively [6]. Other reported anomalies include callosal hypoplasia or agenesis (43%), pyloric stenosis (4.7%), structural eye anomalies (4.1%), cleft palate (2.9%), pulmonary sling with/without tracheal stenosis/hypoplasia (2.9%) [6]. Interestingly, in our case, we found isolated tracheal stenosis without pulmonary sling which is a distinctive finding compared to previous MWS case reviews. Patients usually have moderate to severe intellectual disability with epilepsy [4]. Speech is absent or limited to a few words, with onset at around 5-6 years [6]. Epilepsy has a prevalence of 70-75% and has an age-dependent electroclinical pattern [4]. All types of seizures have been reported. Resistance to antiepileptic drugs was reported in about one-fourth of patients with MWS1,3 but in our case, seizure was well-controlled with anti-epileptic drug monotherapy.

Genetic testing plays an important role in the diagnosis of MWS. Several types of mutations were found including large deletions, frameshift mutations (small deletions/insertions/indels), nonsense mutations, missense mutations, splice site mutations. Among them, the most frequently identified types of mutations were frameshift mutations (46%) and nonsense mutations (37.9%) [2]. In our case we found nonsense mutation of ZEB2 gene on exon 8 leading to nucleotide change (c.2083C>T) with a stop codon (p.Arg695*) and thus causing protein truncation.

In conclusion, MWS is a rare genetic syndrome with a distinctive phenotype caused by mutations in ZEB [2]. Interestingly, in our case, we found isolated tracheal stenosis without pulmonary artery sling which is a distinctive finding compared to the previous MWS case reviews. Better understanding of this genotype-phenotype correlation might hopefully aid in early diagnosis of this uncommon syndrome. We also strongly recommend early evaluation and assessment of airway so as to provide earlier and better treatment and prevention of any anticipated severe airway complications and thus looking forward to offering more comprehensive care for the patients and family support in the future.

Conflict of Interest

The authors have no conflict of interest to declare.

Author's Contributions

Dr. Lun Chin Lin and Dr. Peir Taur Chen drafted the initial manuscript.

Dr. Wan Hsin Wen, Dr. Ni-Chung Lee, Dr. En Ting Wu, Dr. Kai-Chi Chang and Dr. Leticia B. Sy reviewed and revised the manuscript.

All authors contributed to acquisition of case details and the analysis and interpretation of them.

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

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