HK J Paediatr (new series) 2023;**28**:238-242

Case Report

Challenges in the Management of an Infant with Matthew Wood Syndrome Having Pulmonary Hypoplasia and Visual Impairment

KL ***Wong***, WKY ***Chan***, KL ***Siu***

Abstract ***Introduction:*** Matthew Wood syndrome (MWS) is a rare entity in which the two main characteristics include anophthalmia and pulmonary hypoplasia. Other problems such as diaphragmatic eventration, duodenal stenosis, pancreatic malformations, intellectual disability, cardiovascular abnormalities, and intrauterine growth retardation have also been reported. ***Case:*** We report a five-year-old boy who had MWS diagnosed in the neonatal period presenting with bilateral microphthalmia, bilateral pulmonary hypoplasia, diaphragmatic eventuation, and congenital cardiac defects. Misalignment between the light-dark cycle and the endogenous circadian timing causes circadian rhythm sleep disorder (CRSD) – non-entrained type. With non-entrained type CRSD, MWS patients might be somnolent during the day while insomnia is experienced at night. Sleep disturbances have a great impact on the quality of life of this group of patients and limit their opportunity of training in the daytime. On the ground that they have visual impairment, cognitive delay and craniofacial dysmorphism, numerous difficulties are encountered during the initiation of non-invasive ventilation. We did not target a perfectly normal blood gas reading as the treatment goal, rather a balance on optimal ventilatory support against safety and patient's comfort are of a pivotal importance. ***Conclusion:*** CRSD in the group of MWS patients and constraint on optimising ventilatory support were important issues in their long-term care.

Key words *Circadian rhythm sleep disorders; Matthew Wood syndrome; Microphthalmia; Pulmonary hypoplasia*

Introduction

Matthew Wood syndrome (MWS) is a rare entity in which the two main characteristics include anophthalmia and pulmonary hypoplasia.[1,2] Other problems such as diaphragmatic eventration, duodenal stenosis, pancreatic malformations, intellectual disability, cardiovascular abnormalities, and intrauterine growth retardation have also been reported.[1,3]

Department of Paediatrics, Queen Elizabeth Hospital, 30 Gascoigne Road, Jordan, Kowloon, Hong Kong SAR, China
KL **Wong** (王健樂) *MBBS(HK), FHKCPaed, FHKAM(Paed)*
WKY **Chan** (陳桂如) *MBBS(HK), FHKCPaed, FHKAM(Paed)*
KL **Siu** (蕭僑樂) *MBBS(HK), FHKCPaed, FHKAM(Paed)*

Correspondence to: Dr KL **Wong**
Email: wkl452@ha.org.hk

Received March 8, 2023

Case Report

This is a full-term Chinese boy born to non-consanguineous parents with unremarkable antenatal history and fetal morphology scan. At birth, chest X-rays showed bilateral small lung volume with elevated diaphragms. Computed tomography (CT) thorax showed a well-formed trachea and main bronchi; however, the right middle lobe was absent and bilateral lung volume was diminished (Figure 1). There was bilateral diaphragmatic eventration without diaphragmatic hernia. These features were suggestive of bilateral pulmonary hypoplasia. The echocardiogram showed atrial septal defect (ASD), ventricular septal defect (VSD) and patent ductus

arteriosus (PDA), complicated with supra-systemic pulmonary hypertension. CT orbit and brain confirmed bilateral microphthalmia with no focal lesion in the brain. With clinical features of microphthalmia, bilateral pulmonary hypoplasia, bilateral diaphragmatic eventration and congenital cardiac abnormalities, clinical diagnosis of MWS was made.

Because of pulmonary hypertension and pulmonary hypoplasia, he required high ventilatory support in addition to the use of inhaled nitric oxide and oral pulmonary vasodilators, including sildenafil and bosentan. Inhaled nitric oxide and oral pulmonary vasodilators could be weaned off in one-month time. Echocardiogram at four months of age detected rebound of severe pulmonary hypertension with the presence of pre-existing heart failure, PDA, ASD and VSD. The child finally underwent VSD closure, PDA ligation, and ASD reduction at half year old. The patient was successfully extubated at eight months old to non-invasive ventilation. Eventually, pulmonary vasodilators were weaned off at one year of age. The patient was discharged home with bi-level ventilator at one and half years old.

Although clinical features were diagnostic of MWS, local genetic test for detection of STRA6 mutation was not available at the time of diagnosis. Overseas genetic test was declined by parents due to financial reason.

Follow-up and Outcome

Four years after discharge, he showed gradual improvement in respiratory status with an increase in ventilator-free time during the wake time. Steady lengthening in daytime sprinting duration up to 12 hours

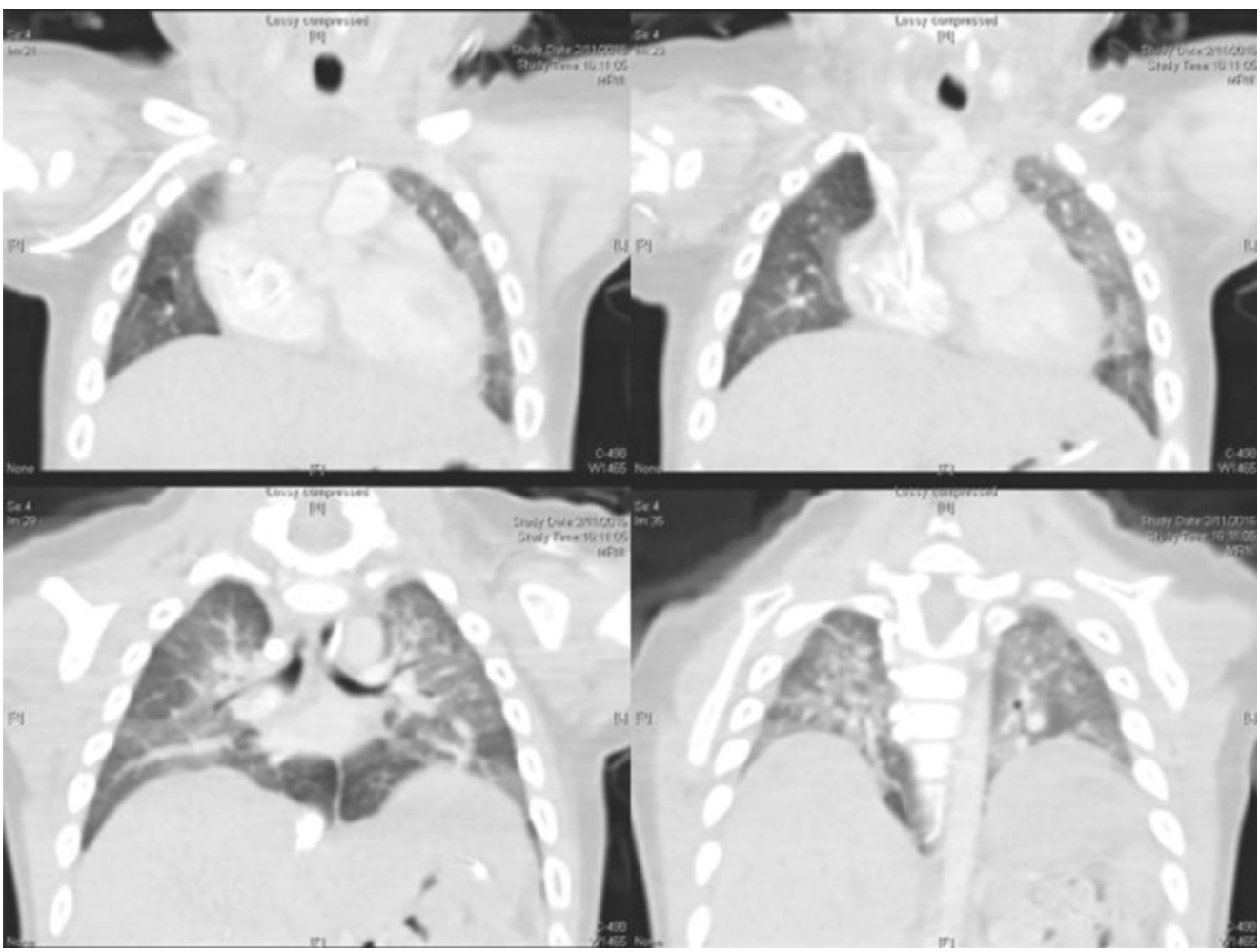

Figure 1 Lung hypoplasia as shown in the CT thorax.

while awake was achieved, but he still required low flow supplemental oxygen at 1 L/min to bi-level ventilator nocturnally. The overnight oximetry and transcutaneous carbon dioxide ($TcCO_2$) monitoring at five years of age showed an average oxygen saturation (SpO_2) at 97.6% and $TcCO_2$ level ranged 6.7-8.3 kPa. Manual ventilator titration was performed to achieve an optimal setting at inspiratory pressure of 19 cmH_2O, expiratory pressure of 7 cmH_2O, using a home ventilation machine (PrismaVENT 30) at S/T mode. The residual apnea-hypopnea index was 2 events per hour. The average SpO_2 was 97%. The highest $TcCO_2$ was 59 mmHg with $TcCO_2$ greater than 50 mmHg in more than half of the sleep duration.

Multiple challenges have been come across when managing this boy. Among these, the worth discussing points was to address his very irregular sleep-wake cycle secondary to his severe visual impairment. Although the ideal aim was to achieve a normal sleep-wake cycle with sustained nocturnal sleep, he could only enjoy fragmented short sleep for three to four hours in each nap period. The measure to ameliorate this challenge included the use of regular oral hypnotics. Melatonin at the dose of 3 mg was supplemented to regulate the patient's sleep cycle.

Discussion

A case of MWS was presented. MWS is also known as Spear syndrome,[4] PDAC (pulmonary hypoplasia/agenesis, diaphragmatic hernia/eventration, anophthalmia/microphthalmia, and cardiac defect) syndrome or microphthalmic syndrome 9 (MCOPS 9, OMIM601186),[5] which is a rare medical condition. This set of disease entity was first reported back in the 1970s.[6] The name "Matthew Wood" was used after the name of the family with two children presenting with bilateral anophthalmia and pulmonary hypoplasia.[7] After the study of 8 patients by Chitayat et al, it was proposed the syndrome to be named PDAC (Table 1).[8]

Due to the fatal outcome of this syndrome, most case reports were based on autopsy findings. There were only a few cases reporting survival beyond infancy period, among which only one adolescent patient reached age 14.[9] Owing to the limited lifespan of most patients, no studies have focused on the long term management. Amidst the possible obstacles, we would like to emphasize discussion on the topic of circadian rhythm sleep disorder (CRSD) and ventilation difficulty in survivors.

Normal circadian rhythm requires internal control at the hypothalamus and light exposure to the eyes.[10] The time of the light exposure can alter phase advance or phase delay of the sleep-wake cycle. Misalignment between the light-dark cycle and the endogenous circadian timing, as in blind people, causes CRSD – non-entrained type. One study reported 87% of the blind people suffered from at least one sleep problem, compared with 30% in the sighted people group.[11] CRSD is an indispensable subject to be addressed in MWS long-term survivors, because they are meant to participate in daily activities, daytime schooling, and training when they grow up. With non-entrained type CRSD, MWS patients might be somnolent during the day while insomnia is experienced at night. Although there is no international guideline for the treatment of CRSD in visually disturbed people, a systemic review suggested that melatonin and tasimelteon might cause entrainment and improve subjective sleep measures with limited side effects.[12] In our patient, melatonin was introduced at around 21 months of age to prepare for his school entry. Nevertheless, only a brief benefit of lengthened sleep duration by an hour was observed, yet without entrainment to normal sleep-wake cycle. Further studies shall be done in this field as sleep disturbances have a great impact on the quality of life of this group of patients and limit their training opportunity.

Non-invasive ventilation is another big challenge in the long-term care plan for MWS patients. On the ground that they have visual impairment, cognitive delay and craniofacial dysmorphism, numerous difficulties are encountered during the initiation of non-invasive ventilation. There were confined facial contact points where an interface could be put on. For our patient, only a single brand nasal mask fit him. Consequently, our patient had developed midface hypoplasia with chronic use of positive pressure ventilation on one single mask interface, in addition to the contribution by the poor development of the globes (Figure 2). These patients usually demonstrate great agitation when being put on non-invasive ventilation, for the reason that they cannot see the appliances. Another technical difficulty on non-invasive ventilation titration is the pressure setting. Considering the factors of pulmonary hypoplasia with reduced lung compliance, easy agitation, and disturbed sleep-wake cycle, a mutually beneficial approach in achieving optimal ventilatory support with normal blood gas parameters, and good quality of life and safety is definitely not an easy task. The latest manual ventilator titration of our patient was performed at five years of age. Permissive hypercapnia approach was adopted. Further increase in pressure support settings was

Table 1 Comparison between reported features of Matthew Wood syndrome and our case

Our case	Reported case
Respiratory	
Pulmonary hypoplasia	Pulmonary hypoplasia / agenesis[4,6,7]
Diaphragmatic eventuation	Diaphragmatic eventuation / hernia[4,8]
Respiratory failure on ASD	
Circadian-rhythm sleep disorders	
Cardiac	
ASD, VSD, PDA	VSD, PDA[3,4,8]
	Conotruncal or great-artery malformations[9]
Endocrine	Congenital primary hypothyroidism
Gastrointestinal	
Gastroesophageal reflux	Pancreatic malformation[3]
Feeding problem on gastrostomy feed	
Aspiration	
Neurological	
Hypoplastic globe (Figure 3)	Anophthalmia / microphthalmia[7]
Hypoplastic optic nerves	Ocular dysplasia[8]
Developmental delay	
Mild conductive hearing deficit	

ASD: atrial septal defect; VSD: entricular septal defect; PDA: patent ductus arteriosus

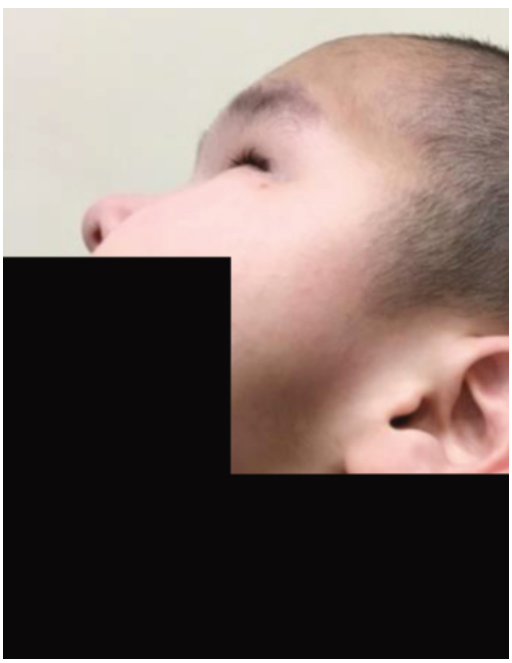

Figure 2 Midface hypoplasia with chronic positive ventilation use.

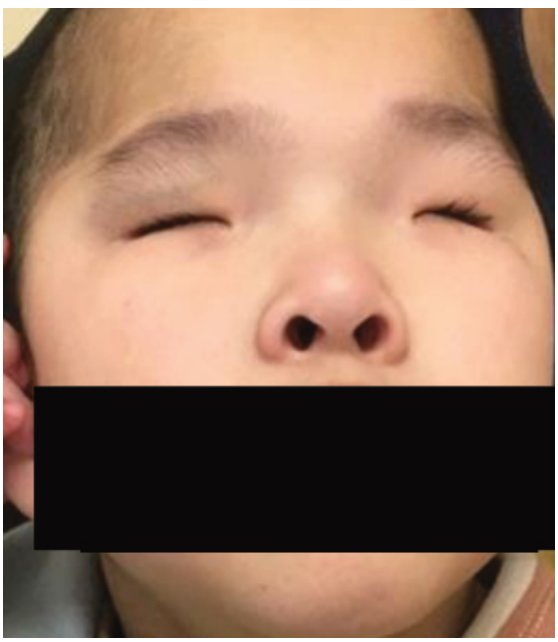

Figure 3 Bilateral hypoplastic globe.

restricted by an increase in arousals and the risk of pneumothorax, especially in the context of pulmonary hypoplasia. As a consequence, we did not target a perfectly normal blood gas reading as the treatment goal, rather a balance on optimal ventilatory support against safety and patient's comfort were of our pivotal importance.

Conclusion

MWS remains a rare disease entity with a variable presentation and prognosis. Main clinical features include anophthalmia/microphthalmia and pulmonary hypoplasia or agenesis. CRSD in this group of visually impaired patients and constraint on optimising ventilatory support are important issues to take care, and they are not thoroughly discussed in the literature. Further reports focusing on these aspects shall potentiate treatment benefits.

Acknowledgement

All radiological images and clinical photos in the manuscript have been consented by the patient's legal guardian.

Conflict of Interest

All authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Funding

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

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