Annals of Clinical and Medical Case Reports

Case Report ISSN 2639-8109 | Volume 9

A Novel Case of CASK-Related Microcephaly with Pontine and Cerebellar Hypoplasia Complicated by Airway Disorders

Shah MA[1*], Szadek LL[2] and Gonzalez T[3]

[1]Department of Internal Medicine, Banner University Medical Center, Phoenix, USA

[2]Department of Pediatrics, Prisma Health Richland, Columbia, SC, USA

[3]Palmetto Pediatrics, North Charleston, SC, USA

[*]Corresponding author:

Milaan Shah,
Department of Pediatrics, Prisma Health Richland, Columbia, SC, 1111 E. McDowell Road, Phoenix, AZ 85006, USA, E-mail: Milaan8697@gmail.com

Received: 21 Jun 2022
Accepted: 05 Jul 2022
Published: 11 Jul 2022
J Short Name: ACMCR

Citation:

Shah MA, A Novel Case of CASK-Related Microcephaly with Pontine and Cerebellar Hypoplasia Complicated by Airway Disorders. Ann Clin Med Case Rep. 2022; V9(9): 1-3

Keywords:

Pontine and cerebellar hypoplasia; Nystagmus

1. Abstract

CASK-related disorders are a group of rare, neurodevelopmental disorders precipitated by mutations in the CASK gene. MICPCH, a rare form of CASK-related intellectual disability, can present with epilepsy, nystagmus, microcephaly, pontine and cerebellar hypoplasia, and hypotonia. However, an association between MICPCH and airway and/or laryngeal disorders has not been previously documented or established. Thus, we present a case highlighting the presentation and diagnosis of MICPCH in a newborn female, which was further complicated by numerous airway and laryngeal disorders.

2. Introduction

CASK-related disorders are a group of rare, neurodevelopmental disorders precipitated by mutations in the CASK gene, a protein coding gene involved in brain development and neuronal signaling [1, 2]. CASK-related disorders include CASK-related intellectual disability, X-Linked Mental Retardation (XLMR), autism spectrum disorders, and FG syndrome [2-4]. CASK-related intellectual disability has two main forms, Microcephaly with Pontine and Cerebellar Hypoplasia (MICPCH) and X-Linked Intellectual Disability (XLID) [1, 5]. MICPCH is caused by an X-linked loss-of-function mutation in CASK and can present with intellectual disability, epilepsy, nystagmus, microcephaly, pontine and cerebellar hypoplasia, and hypotonia [1, 6]. MICPCH is exceedingly rare with only 60 total cases described in the literature to date [7]. With the nonspecific findings and wide variation in presentations of MICPCH, the differential diagnosis in patients with this condition is broad. Thus, we present a case highlighting the presentation and diagnosis of MICPCH in a newborn female, which was further complicated by numerous airway and laryngeal disorders.

3. Case Report

The following case reviews a newborn female who was evaluated for microcephaly plotting at < 1st percentile. Microcephaly was noted as early as 20 weeks on prenatal ultrasound, but otherwise, she was born at term with a normal newborn course. A preliminary CR Skull showed a proportional skull shape despite microcephaly and patent sagittal, lamboid, and coronal sutures. The microcephaly raised concern for possible Zika virus or a TORCH infection given potential exposure to parvovirus B19 while pregnant and URIs at 16 and 30 weeks of gestation, one of which was influenza, but all testing for concerned infections returned negative. Initial eye exam revealed mild bilateral myopia and astigmatism.

Early on, the patient met developmental and growth milestones, but at three months of age, she started to fall behind on her weight and height growth curves, and by six months of age, she began missing milestones and displayed signs of developmental delay. Given her failure to thrive and microcephaly, an MRI of the brain was performed, which showed absence of the inferior cerebellar vermis and inferior half of the right and left cerebellar hemispheres and hypoplasia of the pontine. Genetic testing revealed a c.79C>T

(p.Arg27*) nucleotide change of the CASK gene on Xp11.4 and a microarray gain 13q12.11 VUS. The combination of the MRI findings and genetic testing confirmed the diagnosis of MICPCH.

Throughout the patient's first few years of life, she had multiple ENT/airway issues, including dysphagia, laryngomalacia, stridor, sleep apnea, recurrent otitis media, and tonsillar hypertrophy. From birth, she had noisy breathing, which was exacerbated by multiple bouts of upper respiratory infections that required trips to the Emergency Department for increased work of breathing in the first six months of life. Given the concerns surrounding her breathing, she underwent a sleep study that showed evidence of obstructive sleep apnea. An adenoidectomy was performed at 11 months of age. However, after minimal improvement in her disordered breathing, she also had a supraglottoplasty. Despite these two procedures, a repeat sleep study at 18 months showed worsening sleep apnea, and she was started on nocturnal oxygen supplementation.

Simultaneously, the patient was having progressive feeding difficulties, including significant spillage, choking, and stridor. She had a G-tube placed and underwent Nissen fundoplication, after which her weight gradually improved. In addition, her disordered breathing symptoms improved following these procedures, likely due to the decreased reflux which may have been exacerbating her apnea. Six months after the G-tube placement and Nissen fundoplication, her sleep apnea exacerbated, and a tonsillectomy was performed. Her most recent sleep study still showed mild sleep apnea, but the results were improved from her previous two studies. To date, she is progressing well clinically and continues to be followed by pediatric genetics, neurology, ophthalmology, and endocrinology. She awaits further assessment by aerodigestive specialist to better characterize the relationship between her GI and airway complications.

4. Discussion

MICPCH is a rare genetic condition causing progressive microcephaly. Although it is uncommon, MICPCH should be considered in the differential diagnosis of congenital microcephaly, especially with concomitant seizures or when no obvious etiology causing microcephaly is present. While microcephaly can be caused by infectious etiologies, it is estimated that 33% of cases of microcephaly are caused by a genetic anomaly [8]. In this case, testing for infectious agents, including zika virus, parvovirus B19, rubella, and CMV, all returned negative. Genetic testing and brain imaging eventually revealed the cause of the microcephaly. Once other causes of microcephaly are eliminated, genetic precipitants of microcephaly, such as MICPCH, should be strongly considered.

Sleep apnea, laryngomalacia, and tonsillar hypertrophy are not known to be associated with MICPCH and, to our knowledge, have not been documented in any other cases of MICPCH. Although the cause of her airway/laryngeal disorders are unknown, practitioners should remain aware of the potential for airway complications in patients with MICPCH. Furthermore, in this case, it seems likely that there is some association between the underlying GI issues and airway complications. The anomaly relating the two conditions is currently unknown and will be assessed further in the near future.

In cases of suspected MICPCH, referral to genetics and early, comprehensive genetic testing are integral in determining the diagnosis and developing an appropriate treatment plan. Estimates suggest that 40% of patients with MICPCH will present with seizures by the age of 10 and up to 29% will develop nystagmus [1, 6]. There is no definitive treatment for MICPCH so treatment is largely based on the management of symptoms. The integration of multiple medical specialties into the care team is critical for monitoring and managing current and emerging symptoms [1]. In this case, subspecialities such as pediatric endocrinology and surgery were able to help address delays in growth, and procedures performed by otolaryngologists helped correct airway problems. Ongoing monitoring by neurology and ophthalmology will help identify and treat possible seizure activity or nystagmus and strabismus, respectively.

After a thorough review of the literature, the c.79C>T (p.Arg27*) nonsense mutation of Xp11.4 has previously been associated with two individual cases of MICPCH [9]. In both cases, it is believed that the c.79C>T (p.Arg27*) point mutation was responsible for the phenotypic presentation. To date, a microarray gain 13q12.11 VUS has not been identified in the literature, and it is unclear what clinical significance this mutation holds. Inheritance through germline mosaicism is theoretically possible, but it would be exceedingly rare, and given the two previously identified cases of MICPCH with this mutation, the lack of MICPCH in both of the patient's parents, and autosomal dominant expression pattern of CASK mutations, the patient likely developed MICPCH due to a de novo CASK mutation [1].

References

1. Moog U, Uyanik G, Kutsche K. CASK-Related Disorders. GeneReviews. 2013.
2. CASK gene: MedlinePlus Genetics. Medlineplus.gov. August 10, 2020. Accessed August 30, 2021;
3. Hackett A, Tarpey PS, Licata A, et al. CASK mutations are frequent in males and cause X-linked nystagmus and variable XLMR phenotypes [published correction appears in Eur J Hum Genet. 2010; 18(5):544-552.
4. Neale BM, Kou Y, Liu L, et al. Patterns and rates of exonic de novo mutations in autism spectrum disorders. Nature. 2012; 485(7397): 242-5.
5. CASK-related intellectual disability. Genetics Home Reference. 2014.
6. CASK-Related Disorders. Rarediseases.info.nih.gov. March 2017. 2022.
7. Shinshu University. (2019, February 15). Looking behind a rare brain disease for clues to treat more common mental disorders: Researchers use genetic manipulation techniques to highlight how the function of a protein can lead to neurodevelopmental delays. Sci-

enceDaily. 2021.

8. von der Hagen M, Pivarcsi M, Liebe J, et al. Diagnostic approach to microcephaly in childhood: a two-center study and review of the literature. Dev Med Child Neurol. 2014; 56(8): 732-741.
9. Hayashi S, Uehara DT, Tanimoto K, et al. Comprehensive investigation of CASK mutations and other genetic etiologies in 41 patients with intellectual disability and microcephaly with pontine and cerebellar hypoplasia (MICPCH). PLoS One. 2017; 12(8): e0181791.