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Abstract

Osteopathia striata with cranial sclerosis (OSCS) is a rare skeletal dysplasia inherited in an X-linked dominant pattern. Patients present with a wide variety of congenital anomalies such as craniofacial, cardiac, musculoskeletal, intestinal, and genitourinary abnormalities, and developmental delay. The genetic mutation causes increased ossification of bones which can compress cranial nerves and subsequently lead to acquired hearing loss, facial paralysis, and other neurologic defects. OSCS has also been associated with epileptic seizures, pyloric stenosis, hypothyroidism, and increased bone fragility. Due to the nonspecific presentation of conditions like OSCS and the serious complications it predisposes patients to, it is important that children undergo early genetic testing to confirm the diagnosis of such conditions. Genetic testing and similar services are especially limited in rural and underserved areas and this significantly impacts patient care, particularly for the pediatric population. This case describes a child with limited access to nearby genetic services presenting with multiple unexplained congenital abnormalities who was ultimately diagnosed with OSCS following genetic testing. It describes the clinical presentation of a rare condition and highlights the significantly protracted process of genetic testing for patients in underserved areas without access to genetic services and why providers must be aware of these healthcare disparities and how they affect patients.

Keywords

access to care; healthcare disparities; rural health; congenital anomaly; genetic testing

Cover Page Footnote

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ABSTRACT

Osteopathia striata with cranial sclerosis (OSCS) is a rare skeletal dysplasia inherited in an X-linked dominant pattern. Patients present with a wide variety of congenital anomalies such as craniofacial, cardiac, musculoskeletal, intestinal, and genitourinary abnormalities, and developmental delay. The genetic mutation causes increased ossification of bones which can compress cranial nerves and subsequently lead to acquired hearing loss, facial paralysis, and other neurologic defects. OSCS has also been associated with epileptic seizures, pyloric stenosis, hypothyroidism, and increased bone fragility. Due to the nonspecific presentation of conditions like OSCS and the serious complications it predisposes patients to, it is important that children undergo early genetic testing to confirm the diagnosis of such conditions. Genetic testing and similar services are especially limited in rural and underserved areas and this significantly impacts patient care, particularly for the pediatric population. This case describes a child with limited access to nearby genetic services presenting with multiple unexplained congenital abnormalities who was ultimately diagnosed with OSCS following genetic testing. It describes the clinical presentation of a rare condition and highlights the significantly protracted process of genetic testing for patients in underserved areas without access to genetic services and why providers must be aware of these healthcare disparities and how they affect patients.

Key words: congenital anomalies, access to care, healthcare disparities, genetic testing

INTRODUCTION

Osteopathia striata with cranial sclerosis (OSCS) is a rare skeletal dysplasia with a prevalence rate of 0.1/1 million people worldwide (Savarirayan et al., 2012). It has been shown to

be associated with a pathogenic variant in the *AMER1* gene, also known as the *WTX* gene (Jenkins et al., 2009), and is inherited in an X-linked dominant pattern (Behninger & Rott, 2000; Rott et al., 2003; Viot et al., 2002). The pathogenic variant is a loss-of-function mutation which ultimately leads to upregulated Wnt signaling promoting bone formation, which can result in cranial sclerosis (Perdu et al., 2010). OSCS affects females to males in a 9:1 ratio and can be lethal in male fetuses *in utero* (Viot et al., 2002). The lower male survivability rates can be explained due to the X-linked nature of this gene. The term *osteopathia striata* refers to the radiologic findings of benign linear striations that may be seen on long bones, bones of the pelvis, and scapulae in affected patients, though affected males rarely have these striations (Perdu et al., 2010).

This condition can cause congenital defects including craniofacial abnormalities such as hypertelorism and macrocephaly, and cardiac abnormalities such as atrial or ventricular septal defects, patent ductus arteriosus, hypoplastic left heart or pulmonary valve atresia (Jenkins et al., 2009; Perdu et al., 2010). Other abnormalities associated with OSCS include intestinal malrotation, nervous system malformation, hydronephrosis, and limb hypoplasia (Jenkins et al., 2009; Rott et al., 2003; Perdu et al., 2010; Holman et al., 2011). This condition also predisposes surviving patients to other medical problems in the future. Acquired hearing loss, facial paralysis and other neurologic defects can occur as a result of compression of cranial nerves due to increased ossification of the skull. Patients commonly experience developmental delay. OSCS has also shown to be associated with epileptic seizures (Rott et al., 2003). Rare documented associations of OSCS also include hypothyroidism, pyloric stenosis, increased bone fragility, and chronic lower extremity pain in the absence of fractures (Rott et al., 2003; Nakamura et al., 1985; Fradin et al., 2016; Ward et al., 2004). There has also been a documented case of genetic mosaicism in OSCS (Joseph et al., 2010).

Due to the nonspecific and variable presentation of this condition, it is crucial for OSCS to be diagnosed early to initiate proper management in a timely manner in order to improve patient outcomes. Proper diagnosis is dependent on genetic analysis and identification of the *AMER1* pathogenic variant. This case characterizes a patient who presented with multiple congenital abnormalities but underwent a delay in receiving genetic testing due to healthcare disparities in an underserved region of the United States, before ultimately being diagnosed with OSCS.

Case Presentation

A 7-month-old male was brought to a primary care pediatrician as a new patient. Upon examination, the child had a large soft anterior fontanelle, apparent macrocephaly, and frontal bossing along with a mild distal penile hypospadias. He demonstrated developmental delay as he was unable to hold his head up or roll over, and only sat upright with tripoding. The child's head circumference was measured at 51.5 cm, in the 99.9th percentile for his age group. A CT scan of the head demonstrated mild prominence of extra-axial cerebrospinal fluid spaces along the frontoparietal lobes and minimal prominence of the lateral ventricles.

The patient was born at a gestational age of 39 weeks and 1 day by normal spontaneous vaginal delivery to a gravida 7 para 6 mother. Prenatal ultrasound had revealed polyhydramnios, suspected macrosomia, and bilateral choroid plexus cysts. On newborn exam, the child was noted to have small ears and macrocephaly. Neonatal ultrasound of the head showed normal ventricles and small bilateral choroid plexus cysts. Records for the patient's previous well child visits at a different clinic noted unspecified developmental delay at four months of age.

After considering the patient's birth and developmental history along with his multiple unexplained congenital anomalies and imaging findings, the primary care pediatrician decided to refer the patient to neurosurgery, who, after evaluation, described the macrocephaly and extra-axial fluid collection as benign. As care continued, the patient's development was as follows: he was able to roll over by 9 months of age; sit upright, pull to stand, and speak first words by 12 months; and crawl by 15 months of age. Head circumference was 51.8 cm (99.9th percentile) at 9 months of age and 53.6 cm at 18 months (99.9th percentile) indicating persistent macrocephaly.

The patient's continued evaluation included several diagnostic studies over the course of his first two years of life. MRI of the head at 11 months of age showed no evidence of hydrocephalus. At 14 months, the child was noted to have an elevated serum creatine kinase level of 239 U/L (reference range < 160 U/L). A chromosomal microarray detected a 72 kb deletion of chromosome 2q37.3 within the intron of the *HDAC4* gene. The patient was referred to a geneticist for further evaluation. The child resided in a county classified by the U.S. Department of Agriculture as a "2" on the Rural-Urban continuum and had to be referred to a larger urban academic center over 400 miles away from his residence for further evaluation. Transportation to this distant facility was an apparent issue, as was scheduling due to this being the only such facility in the entire state. As such, the patient was not seen for further genetic evaluation until over three months later. The provider at the genetic center recommended exome sequencing along with parental testing. Six additional months later, exome sequencing results returned and revealed a *de novo* pathogenic variant, c.1215_1221del (p.Leu406Ilefs*14), in the *AMER1* gene. The child was diagnosed with Osteopathia Striata with Cranial Sclerosis. Due to the patient's limited access to genetic services, the patient was not diagnosed until he neared 2 years of age, even though the initial referral for genetic evaluation was placed nine months before.

DISCUSSION

This patient presented with multiple unexplained congenital abnormalities and developmental delay at 7 months of age and a genetic condition was suspected. Due to travel distances, long wait periods for appointments, financial restrictions, and limited accessibility and availability of genetic counselors in the patient's region of residence, he experienced a protracted process of genetic testing before being diagnosed with OSCS. Due to the nonspecific and variable presentation of OSCS, genetic testing is a pivotal component of patient care as a definitive diagnosis prepares the patient, family, and healthcare providers with knowledge of what to expect over the course of the patient's life and helps guide patient management. Prior knowledge of a genetic condition in this family could have led to targeted intervention and appropriate management of the patient from birth. However, the patient's limited accessibility to genetic testing led to a delay in diagnosis, and he was temporarily lost to follow-up as a consequence of the extensively prolonged workup.

The significance of genetic testing extends beyond the patient as it may impact immediate family members who undergo testing as well. Parental testing can influence future family planning, especially considering the associated risk of *in utero* fetal demise in OSCS. The patient's mother in this case suffered a miscarriage in the past and experienced another one soon after the birth of this patient. The exact etiology of those miscarriages is unknown; however, it is possible the genetic association of OSCS may have been an underlying factor. Prior knowledge of this genetic condition may have been a determining factor in future conceptions for this family, highlighting the broader implications of access to genetic testing.

Genetic variation or abnormality affects an estimated 8% of all live births (Kim & Bodurtha, 2019). Approximately 26% of infants with three or more minor congenital abnormalities have associated major abnormalities (Leppig et al., 1987). Consequently, genetic testing is now being incorporated into preventative medicine and World Health Organization screening guidelines for providers (Fogleman et al., 2019). However, the referral process, long wait times for appointments, travel distances, and time taken to receive results can make genetic testing a significantly drawn-out process. This problem is amplified in rural communities in the United States with limited access to geneticists.

The healthcare deficits in rural areas has been well-documented in primary literature (Hall & Olopade, 2006; US Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau, 2015). Rural areas are especially lacking in genetic counseling services, which greatly affects the early diagnosis of pediatric genetic disorders Emmet et al., 2017). While technical advances have made clinical genetic testing more cost effective, genetic counseling is still difficult to access for patients. Although several studies have shown rural patients are receptive to counseling in any form, whether in person or through telemedicine services, the supply has yet to meet the demand (Fogleman, 2019; Cohen et al., 2013). These issues affect the rural populace as a whole, but it is especially important to consider the consequences that the lack of genetic counseling services has on the pediatric population in particular. There has been a nationwide decline in pediatric mortality in the US since 1999, but a recent study has shown that children in rural areas have not seen that same decline in mortality (Probst et al., 2019). Difficulties in obtaining genetic counseling and other similar highly technical services contribute to this multifactorial problem.

This case reflects the many patients and families who are impacted by the limited accessibility of specialty services such as genetic counseling nationwide, leading to inadequate medical care. It highlights the importance of further research and investment into making these services more accessible for pediatric patients, especially in rural settings, to prevent delays in diagnosis and guide patient management.

CONCLUSION

OSCS is a rare genetic disorder that is diagnosed in early childhood and is associated with multiple comorbidities that increase the risk of developmental abnormalities. Early genetic counseling is paramount to evaluate for suspected OSCS and its associated genetic abnormalities. Limited access to genetic services is a significant barrier to healthcare for many patients, and this problem is only amplified in rural and underserved areas which may lack the services of other pediatric specialties as well. This limited access makes early diagnosis exceptionally more difficult, which can affect both the patient's healthcare outcomes as well as that of the patient's family. Awareness of this disparity is imperative, and measures need to be taken to make pediatric specialty services more accessible to those in rural environments in order to prevent a delay in diagnosis which may lead to adverse health outcomes. As access to a geneticist in rural or underserved areas can take many months if available, it is important that pediatric healthcare providers such as pediatricians and family practitioners are appropriately trained in matters regarding the evaluation and management of patients with dysmorphology and have access to further training regarding genetic counseling and evaluation of patients. Going forward, telemedicine may also play a role in addressing some of these barriers for genetic evaluation in underserved areas and is an option to consider in the future.

REFERENCES

Behninger, C., & Rott, H. D. (2000). Osteopathia striata with cranial sclerosis: literature reappraisal argues for X-linked inheritance. *Genetic counseling (Geneva, Switzerland)*, *11*(2), 157-167.

Cohen, S. A., Marvin, M. L., Riley, B. D., Vig, H. S., Rousseau, J. A., & Gustafson, S. L. (2013). Identification of genetic counseling service delivery models in practice: a report from the NSGC Service Delivery Model Task Force. *Journal of genetic counseling*, *22*(4), 411-421. *doi*:10.1007/s10897-013-9588-0.

Emmet, M., Stein, Q., Thorpe, E., & Campion, M. (2018). Experiences of genetic counselors practicing in rural areas. *Journal of genetic counseling*, *27*(1), 140-154. *doi*:10.1007/s10897-017-0131-6.

Fogleman, A. J., Zahnd, W. E., Lipka, A. E., Malhi, R. S., Ganai, S., Delfino, K. R., & Jenkins, W. D. (2019). Knowledge, attitudes, and perceived barriers towards genetic testing across three rural Illinois communities. *Journal of community genetics*, *10*(3), 417-423. *doi*:10.1007/s12687-019-00407-w.

Fradin, M., Collet, C., Ract, I., Odent, S., & Guggenbuhl, P. (2017). First case of osteopathia striata with cranial sclerosis in an adult male with Klinefelter syndrome. *Joint Bone Spine*, *84*(1), 87-90. *doi*:10.1016/j.jbspin.2016.04.012.

Hall, M. J., & Olopade, O. I. (2006). Disparities in genetic testing: thinking outside the BRCA box. *J Clin Oncol*, *24*(14), 2197-2203. *doi*:10.1200/JCO.2006.05.5889.

Holman, S. K., Daniel, P., Jenkins, Z. A., Herron, R. L., Morgan, T., Savarirayan, R., ... Robertson, S. (2011). The male phenotype in osteopathia striata congenita with cranial sclerosis. *American Journal of Medical Genetics Part A*, *155*(10), 2397-2408. *doi*:10.1002/ajmg.a.34178.

Jenkins, Z. A., van Kogelenberg, M., Morgan, T., Jeffs, A., Fukuzawa, R., Pearl, E. …Robertson, S. (2009). Germline mutations in WTX cause a sclerosing skeletal dysplasia but do not predispose to tumorigenesis. *Nature genetics*, *41*(1), 95. *doi*:10.1038/ng.270.

Joseph, D. J., Ichikawa, S., & Econs, M. J. (2010). Mosaicism in osteopathia striata with cranial sclerosis. *The Journal of Clinical Endocrinology & Metabolism*, *95*(4), 1506-1507. *doi*:10.1210/jc.2009-2343.

Kim, A. Y., & Bodurtha, J. N. (2019). Dysmorphology. *Pediatrics in review*, *40*(12), 609. *doi*:10.1542/pir.2018-0331.

Leppig, K. A., Werler, M. M., Cann, C. I., Cook, C. A., & Holmes, L. B. (1987). Predictive value of minor anomalies. I. Association with major malformations. *The Journal of pediatrics*, *110*(4), 531-537. *doi*:10.1016/S0022-3476(87)80543-7.

Nakamura, T., Yokomizo, Y., Kanda, S., Harada, T., & Naruse, T. (1985). Osteopathia striata with cranial sclerosis affecting three family members. *Skeletal radiology*, *14*(4), 267-269. *doi*:10.1007/BF00352617.

Perdu, B., Freitas, F. D., Frints, S. G., Schouten, M., Schrander-Stumpel, C., Barbosa, M., … Van Hul, W. (2010). Osteopathia striata with cranial sclerosis owing to WTX gene defect. *Journal of Bone and Mineral Research*, *25*(1), 82-90. *doi*:10.1359/jbmr.090707.

Probst, J., Zahnd, W., & Breneman, C. (2019). Declines in pediatric mortality fall short for rural US children. *Health Affairs*, *38*(12), 2069-2076. *doi*:10.1377/hlthaff.2019.00892.

Rott, H. D., Krieg, P., Rütschle, H., & Kraus, C. (2003). Multiple malformations in a male and maternal osteopathia strata with cranial sclerosis (OSCS). *Genetic counseling (Geneva, Switzerland), 14*(3), 281-288.

Savarirayan, R & Stark, Z. (2012). Osteopathia striata-cranial sclerosis syndrome. *Orphanet Encyclopedia*. Retrieved April 4, 2020, from https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=en&Expert=2780.

US Department of Health and Human Services. (2015). The Health and Well-Being of Children in Rural Areas: A Portrait of the Nation, 2011–2012. *US Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau. https://mchb. hrsa.gov*.

Viot, G., Lacombe, D., David, A., Mathieu, M., de Broca, A., Faivre, L., ... & Cormier-Daire, V. (2002). Osteopathia striata cranial sclerosis: Non-random X-inactivation suggestive of X-linked dominant inheritance. *American journal of medical genetics, 107*(1), 1-4. *doi*: 10.1002/ajmg.10028.

Ward, L. M., Rauch, F., Travers, R., Roy, M., Montes, J., Chabot, G., & Glorieux, F. H. (2004). Osteopathia striata with cranial sclerosis: clinical, radiological, and bone histological findings in an adolescent girl. *American Journal of Medical Genetics Part A*, *129*(1), 8-12. *doi*:10.1002/ajmg.a.30107.