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Clinical Conundrum: Polyhydramnios as a Marker for a Fetal Genetic Syndrome in the Canadian Old Order Mennonite Population

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ABSTRACT

A 35-year-old woman was referred to genetics for 2 soft markers but was also found to have polyhydramnios. The couple were Old Order Mennonite, and carrier testing allowed for targeted investigation of syndromes associated with polyhydramnios in this population. Both parents were carriers of a 7304 bp deletion in the *STRADA* (*LYK5*) gene, causing an autosomal recessive syndrome of polyhydramnios, megalencephaly, and symptomatic epilepsy. This led to early recognition and treatment of neonatal seizures. Targeted testing can significantly shorten the diagnostic odyssey and decrease the cost of investigations, an especially important consideration for families who do not accept health insurance.

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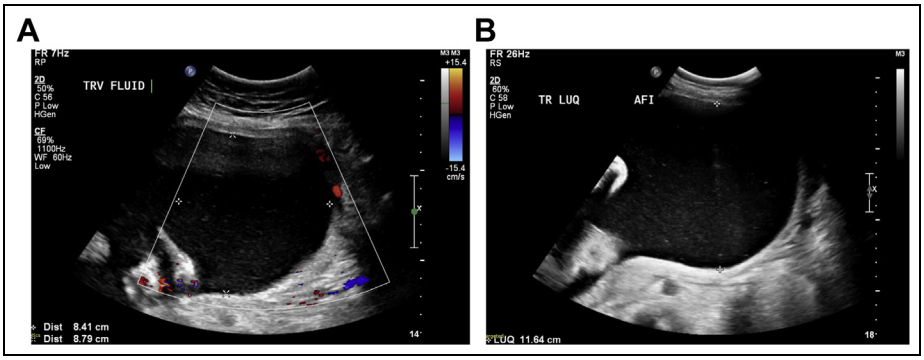
CLINICAL PRESENTATION

A 35-year-old G2 P1 woman was referred to medical genetics for 2 soft markers, choroid plexus cysts and single umbilical artery. The anatomy was otherwise reported as normal with normal amniotic fluid. The couple were third cousins of Old Order Mennonite (OOM) background and had declined first trimester prenatal genetic screening. The pregnancy had otherwise been uncomplicated. The patient was healthy and taking escitalopram for depression. At 20^{3} weeks, the patient had a detailed level II ultrasound showing choroid plexus cysts, single umbilical artery, normal growth, partially clenched hands not seen to open, right renal pelvis measuring 4 mm anterior-posterior, and polyhydramnios with a deepest vertical pocket (DVP) of 8.8 cm (Figure A).

Clinician's Commentary

Given the 2 soft markers, counselling for the increased risk of aneuploidy was performed and screening by non-invasive prenatal testing (NIPT) or diagnosis by amniocentesis was discussed. The patient chose NIPT. Although the majority of mild polyhydramnios cases are idiopathic, the index of suspicion for an underlying pathology should be heightened when presentation occurs before the third trimester. The 2 most common pathologic causes are maternal diabetes mellitus and fetal anomalies.[1] Fetal anomalies are related to impaired swallowing or overproduction of fetal urine secondary to a high-output cardiac state, renal abnormality, or osmotic fetal diuresis. Targeted ultrasonography is

Figure. Ultrasound image of the deepest vertical pocket at (A) 20^3 and (B) 31^2 weeks gestational age.



recommended to assess for fetal abnormalities and growth. Polyhydramnios may be associated with fetal growth restriction or macrosomia. If the fetus is structurally normal, investigations should then screen for diabetes, alloimmunization, and potentially congenital infection. In this case, the hands appearing clenched was concerning for a neuromuscular disorder. Additionally, the risk for autosomal recessive conditions is increased with the parents being consanguineous. Owing to small founder populations and cultural isolation, the Anabaptist groups, including Mennonite, Hutterite, and Amish populations, have many unique genetic disorders, particularly autosomal recessive conditions.[2] A genetic disorder database for the OOM and Amish populations has been established (http://www.biochemgenetics.ca/plainpeople/),[3] and conditions associated with polyhydramnios are outlined in the Table. Carrier screening in the OOM population has been available for 8 disorders through the biochemical genetics laboratory at London Health Sciences Centre in London, Ontario, since 2016. This was discussed and ordered for this patient and her partner.

THE DIAGNOSTIC PROCESS

Follow-up ultrasound at 24^2 weeks showed subjectively increased amniotic fluid but a DVP <8 cm. Hands again were not seen to open, and growth was normal. NIPT was low risk for trisomy 21, 13, and 18; monosomy X; and triploidy. The patient was then referred to a community obstetrician from midwifery, and DVP was 10 cm at 28^2 weeks. Genetic screening for the OOM population identified both the patient and her partner as carriers of a pathogenic 7304 bp deletion in the *STRADA* (*LYK5*) gene, and these results were discussed with the couple at 31^2 weeks. Growth at this appointment was normal, DVP was 11.6 cm (amniotic fluid index 28.5 cm; Figure B), and the left hand was seen to fully open but the right was more consistently clenched.

Clinician's Commentary

Pathogenic variants in the *STRADA* (*LYK5*) gene, causing an autosomal recessive syndrome of polyhydramnios, megalencephaly, and symptomatic epilepsy (PMSE), were first reported in the OOM community in 2007.[4] The current pregnancy had a 25% risk of being affected since the parents were carriers, but the index of suspicion was raised much higher given the polyhydramnios and clenched hands. Out of the current reported cases, all have had polyhydramnios documented during the pregnancy and severe psychomotor retardation and hypotonia after delivery. The etiology of polyhydramnios in this condition is related to the association with diabetes insipidus or decreased swallowing as a result of neuromuscular dysfunction. In reported cases of PMSE, premature labour occurred between 25 and 36 weeks gestation in 75% of pregnancies. In addition to these features, affected children have large heads and infantile-onset intractable multifocal seizures. In a small cohort of 16 children with this disorder, about a third died in childhood (7 months to 6 years of age) from complications of the disorder, including status epilepticus, congestive heart failure due to atrial septal defect, and hypernatremic dehydration due to diabetes insipidus.

TREATMENT AND MANAGEMENT

A presumptive diagnosis of PMSE was discussed with the parents, and delivery in a tertiary hospital was recommended given the risk of neonatal complications.

Table. Syndromes associated with polyhydramnios in the Mennonite and Amish populations

Disorder	Population	Gene	Prenatal ultrasound findings	Neonatal findings and outcome/ treatment	Management based on presumptive diagnosis
PMSE OMIM#611087	OOM	*STRADA*[4]	Polyhydramnios, macrocephaly, hypertelorism, congenital heart disease	Hypotonia, long face, peaked eyebrows, broad nasal bridge, large mouth with thick lips, prominent central forehead in childhood, seizures, developmental delay	Potential therapy with sirolimus for seizures[6]
Congenital central hypoventilation syndrome	Amish	Gene not yet identified	Polyhydramnios, dolichocephaly, brachydactyly	Corneal clouding, prominent occiput, widely separated sagittal sutures, open metopic suture, deep-set small eyes, horizontal crease over nasal bridge, low-set posteriorly rotated ears, bulbous nose, loose skin, lethal in first year of life	Lethal in the first year of life and consideration given for palliative care
Congenital sodium diarrhea OMIM#270420	Amish	*SPINT2*[9]	Polyhydramnios	Diarrhea, metabolic acidosis, hyponatremia (secondary to fecal sodium losses), anal atresia, choanal atresia, corneal erosions, preauricular pits	Plan to deliver in a tertiary care hospital in view of possible choanal atresia and also the need for prolonged total parenteral nutrition
Restrictive dermopathy OMIM#275210	OOM, Old Colony Mennonite, Hutterite	*ZMPSTE24*[10]	Polyhydramnios, intrauterine growth deficiency, arthrogryposis, micrognathia, rocker bottom feet	Tight and rigid skin with erosions, epidermal hyperkeratosis, cutaneous telangiectasia, microstomia, sparse hair for eyelashes and eyebrows, ossification abnormalities, thin dysplastic clavicles, pulmonary hypoplasia, joint limitation and/or contractures	Neonatally lethal due to respiratory insufficiency; prepare for palliative care
Bartter syndrome, type 3 OMIM#607364	Amish	*CLCNKB*[11]	Polyhydramnios	Short stature, metabolic alkalosis, hypercalciuria, dehydration, polydipsia, polyuria, hypocalcemia, hypokalemia	Electrolyte supplementation, prostaglandin synthetase inhibitors, angiotensin-converting enzyme inhibitors and potassium-sparing diuretic

OOM: Old Order Mennonite; PMSE: polyhydramnios, megalencephaly, and symptomatic epilepsy.

Clinician's Commentary

A presumptive prenatal diagnosis based on key ultrasound features may be made in the context of the carrier screening results in the parents. Amniocentesis for confirmation of the diagnosis was declined because testing of the baby could be done after delivery. Many members of this population favour simple, holistic approaches and tend to avoid invasive prenatal diagnosis because they do not wish to put the pregnancy at risk for miscarriage. The church doctrine does not support therapeutic abortions.[5] In addition, because of their belief in separation between the church and the state, many community members do not participate in government-supported health insurance and pay out of pocket for medical expenses. Therefore, obstetrical management that was congruent with religious and community beliefs was discussed. Fetal surveillance was recommended, and the increased risk for preterm delivery and malpresentation given the polyhydramnios was discussed. The patient was not a candidate for breech delivery because this condition is associated with large and abnormally shaped heads.

THE OUTCOME

Spontaneous vaginal delivery of a male infant occurred at 36[2] weeks at a community hospital closer to their home. Apgar scores were 7 and 8 at 1 and 5 minutes, respectively. The infant was hypotonic with a birth weight of 2570 g (27th percentile). Shortly after birth, the infant had respiratory distress secondary to meconium aspiration and was admitted to the neonatal intensive care unit. Cord blood was collected and sent to the biochemical genetics laboratory for *STRADA* gene testing. On day 3, the baby was identified as homozygous for the 7304 bp deletion, supporting a diagnosis of PMSE. The infant was transferred to a tertiary care hospital on day 4 due to hypernatremia suggestive of diabetes insipidus, a known complication of PMSE. Examination revealed a third fontanelle and squared forehead with prominent triangular chin. Palpebral fissures were downslanting, eyes were wide-spaced with a high, wide nasal bridge and slight deviation of the nasal tip to the right. Ears were flattened superiorly. There was a poor suck and micrognathia. Deep tendon reflexes were 2+ and brisk, and both knees had anterior drawer sign. Echocardiogram showed a small patent ductus arteriosus, mild tricuspid regurgitation, and cloverleafed aortic valve. At 4 months, the baby developed seizures and was failing to thrive. Sirolimus and vigabatrin were started, and the seizures remitted. At 6 months of age, a ventriculoperitoneal shunt was inserted for a communicating hydrocephalus. Unfortunately, at 11 months, the child presented with overwhelming sepsis and purpura fulminans and died shortly thereafter.

Clinician's Commentary

In PMSE, seizures are reported to start between 3 and 7 months of age. The *STRADA* gene is an upstream inhibitor of mTORC1. The use of sirolimus, an mTOR inhibitor, has been shown to decrease the frequency or prevent the onset of seizures when started early in infants with PMSE.[6] In addition, some improvement in receptive language was noted in the 5 individuals reported originally. Rapid confirmation of diagnosis in this case facilitated anticipation of seizures and institution of specific targeted treatment (personalized medicine). Unfortunately, long-term side effects of sirolimus include immunosuppression, which may have contributed to the sepsis and death of this infant.

CONCLUDING THOUGHTS

Fetal ultrasound findings in pregnancy offer a unique opportunity for prenatal diagnosis and population-specific counselling. A recognition of syndromes based on key ultrasound features is needed for providers caring for isolated populations because it may add specific syndromes into the differential diagnosis that are extremely rare in the general population. Targeted testing can significantly shorten the diagnostic odyssey and decrease the cost of investigations, an especially important consideration for families who do not accept health insurance. Examples of other prenatal ultrasound findings in the Amish, Mennonite, and Hutterite populations searchable on the database include oligohydramnios, microcephaly, and macrocephaly, among others.

Although Amish and Mennonite communities generally do not accept invasive prenatal diagnosis methods, carrier screening is acceptable and can increase the probability of a diagnosis in a fetus in whom prenatal ultrasound findings will give clues. Directed testing can then be done rapidly at birth. Early birth plans can be made that incorporate the cultural beliefs and practices of the mother. For example, if a known lethal syndrome is likely, based on ultrasound findings and prenatal testing, lengthy hospitalization of the mother may be avoided, and the benefits or risks of a homebirth or delivery at a centre closer to the patient's residence (both including palliative care for the infant) may be discussed. Furthermore, for potentially treatable diseases, rapid diagnosis and treatment can significantly improve outcomes. Mennonite and Amish women often delay or limit necessary reproductive-related health services,[7] although the use of medical technology will be accepted if it is congruent with beliefs and will support and maintain their way of life.[8] Within the populations, there is individual variability in response to pregnancy and childbirth.[8] Generalizations about this group should not be made because some use technology whereas others do not, and there should be detailed discussion with individual families about their beliefs and practices.

Consent: The woman whose story is told in this case report provided signed permission for its publication.

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