CASE REPORT

Prenatal adrenal calcification: A prenatal sonographic feature of congenital cytomegalovirus infection

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SUMMARY

A case of severe congenital cytomegalovirus infection in a healthcare worker is presented. Fetal adrenal calcification is identified as a sonographic finding. Indications for prenatal screening and some aspects of treatment are discussed.

INTRODUCTION

The prevalence of congenital cytomegalovirus infection (cCMVi) is reported to range from 2.6 to 6.8%.[1] of livebirths with the higher end of the spectrum observed in low socioeconomic countries. Congenital CMV infection is the leading cause of nervous system infection in the newborn. It is one of the leading causes of mental restriction, sensorineural deafness and visual impairment in this group.[2]

CASE REPORT

A 34-years-old frontline healthcare worker was referred to our foetal medicine centre with foetal hydrops at week 21 of gestation. This was a planned pregnancy. She had no medical history of note. Her husband is an alpha thalassemia career. The maternal serum free foetal DNA aneuploidy screening at week 12 was low risk for chromosomes 13, 18 and 21 abnormalities. She had a routine level 1 scan at week 16 with the foetus appearing grossly normal with normal biometric parameters. She felt unwell with sore throat, myalgia and low-grade fever lasting two days after this scan. She spent one day at home. There were no localising symptoms or rash. She was back to work the following day feeling fine. The weekly COVID-19 polymerase chain reaction test for frontline healthcare workers were negative. All frontliners work with full protective gear as per national guidelines at the time. A level 2 scan at 20 weeks suggested hydrops fetalis. She presented to our tertiary centre at week 21.

Ultrasound scan findings of the foetus and its environment at the time of assessment are as follows: 1. Small for gestation age (SGA) with biometry symmetrically under the 5th percentile, 2. Ascites was present, 3. No hydrothorax, 4. No skin oedema, 5. Normal liquor volume, 6. Normal placental echotexture, 7. Foetal movements observed but feeble and reduced, 8. Mild cerebral ventriculomegaly with an atrial diameter of 11 mm, 9. Hepatic calcifications, 10. Middle cerebral artery doppler screening for foetal anaemia was negative, 11. Adrenal gland: bilateral extensive echogenic glands of proportionate size suggestive of calcification. There was no evidence of congenital heart defect or dysrhythmia.

Laboratory tests: Red cell antibody screen negative. Kleihauer negative. Blood film and electrophoresis normal. Parvovirus B19 negative. CMV IgM and IgG positive.

Chromosomal study: The couple agreed to an amniocentesis for chromosomal studies. G-band karyotype was normal. Whole exome sequencing (Perkin Elmer Genomics) did not detect any pathogenic sequence variant or variant of unknown significance.

Placental histology: Plasmacytic villitis with positive immunochemistry indicative of CMV infection.

In utero foetal demise was determined 2 weeks after the visit. A perinatal post-mortem was not done respecting the wishes of the couple.

DISCUSSION

A literature search for prenatal adrenal hyperechogenicity or prenatal adrenal calcification and congenital cytomegalovirus infection (cCMVi) did not yield specific papers linking prenatal sonographic adrenal echogenic abnormalities to cCMVi. Adrenal calcification has mostly been described in the postnatal period secondary to other causes.[3] Postnatal causes include birth trauma, foetal acidosis of varying causes, adrenal haemorrhage, Wolman's disease, Niemann-Pick disease and CMV. Prenatal findings for cCMVi are listed in Table I

We report a case of cCMVi with prenatally evident bilateral adrenal echogenicity most probably being calcification.

Serologic CMV IgM and IgG was detected 5 to 6 weeks after the likely episode of illness. This is despite the patient working in a heightened risk aversion manner during the COVID-19 pandemic. Six weeks is the minimum interval between infection/reactivation and foetal infection that becomes serologically detectable.[5] Avidity studies on the IgG if performed would have shed more light on this aspect of the infection. CMV remains lifelong in those infected and exhibits the similar latency characteristics as other herpesvirus family of viruses.[6] A total of 10 to 20% subsequently experience reactivation of disease albeit in milder fashion. Maternal CMV re-activation is the most common scenario in cases of cCMVi. Re-emergence of IgG and IgM is recognised in CMV re-activation. Anti-CMV IgG avidity (level of binding: IgG-viral binding is weaker after primary than re-activation of CMV) testing may help

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Table I: Common ultrasound findings in cCMVi[4]

	Echogenic bowel	**26%**
Non-cranial	Hepatomegaly	14%
	FGR	10%
	Oligohydramnios	7%
	Ascites	4%
	Liver calcifications	3%
	Enlarged placenta	3%
	Pericardial effusion	1%
	Hydrops	1%
	Club foot	1%
Cranial	Calcifications	18%
	Hydrocephaly	18%
	Microcephaly	10%
	Germinative cyst	7%
	Ventriculomegaly	3%
	Cysts	2%
	Polymicrogyria	1%

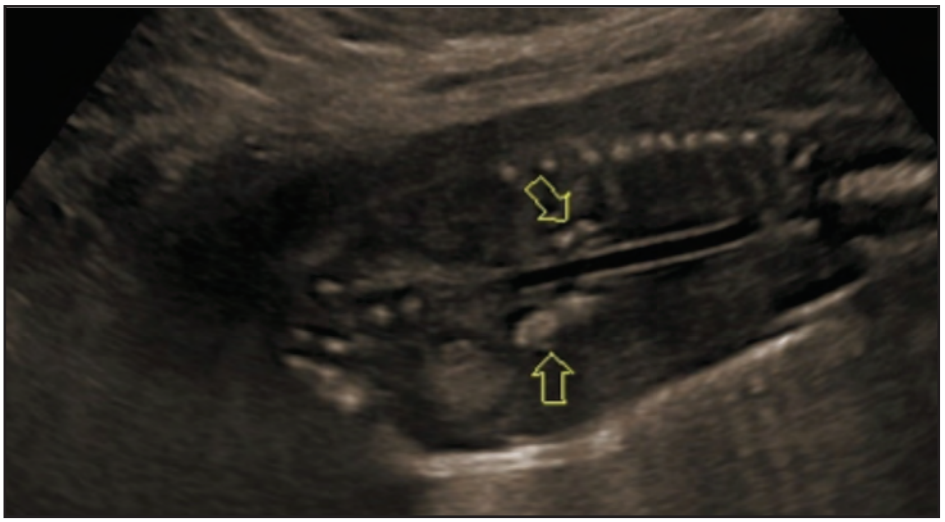

Fig. 1: Large arrows point towards bilateral adrenal hyperechogenicity consistent with calcification

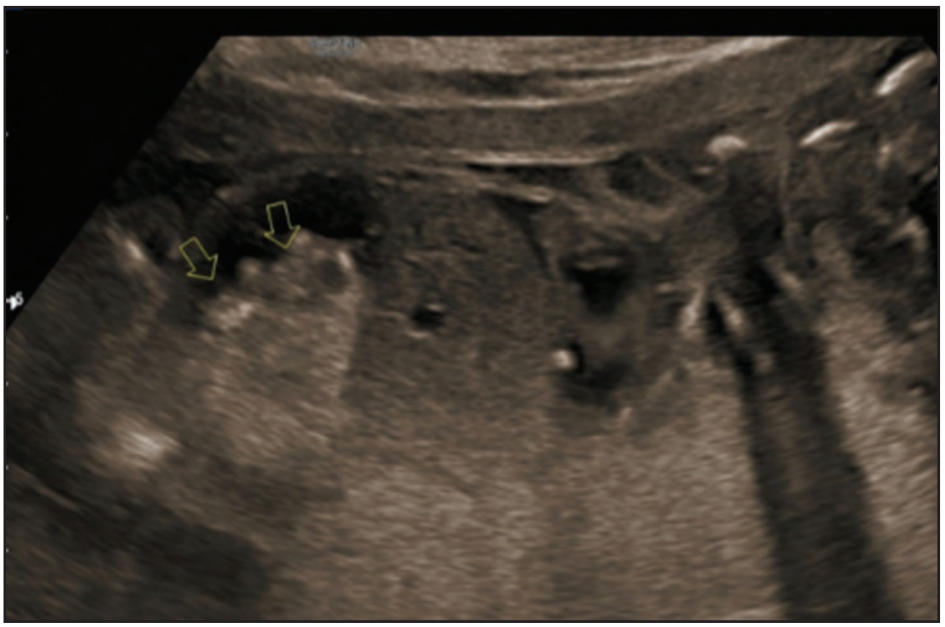

Fig. 2: Large arrows point to echogenic bowel with adjacent ascites.

distinguish primary from a re-activation with high IgG avidity in re-activation cases.[7] Prenatally, amniotic fluid CMV PCR has taken over viral culture as the gold standard for definitive infection as the virus is known to be shed in foetal urine.[8]

It is well known that healthcare workers are at higher risk for CMV infections. Infection requires close contacts with all bodily fluids. Other risk factors for CMV infections include low socioeconomic groups, nursery and childcare settings, and breastfeeding and promiscuity.[9]

CMV screening is currently not routinely recommended even with a prevalence of 2 to 6% of livebirths. CMV infection has a 30 to 40% chance to progress to CMVi and the lack of established treatment is part of why this approach is taken. Furthermore, most cCMVi result in asymptomatic babies. Only 5 to 15% develop symptoms or signs detected prenatally or at birth and this rate is the same in both primary and secondary reactivation cCMVi. Prenatal diagnosis generally confers a poor prognosis. Of babies born with symptomatic cCMVi, 30% will die. In the survivors congenital and perinatal CMV infection remains one of the leading causes of sensorineural deafness, visual impairment and neurologic sequalae including microcephaly, cerebral palsy and neurodevelopmental delay.[10]

CMV can be prevented by simple health measures like sanitising surfaces, use of gloves and hand washing. Serologic screening and surveillance for healthcare workers and other at-risk groups mentioned who are embarking on pregnancy can be recommended. Healthcare workers embarking on pregnancy should have CMV serology baseline taken at booking. Serologic surveillance at regular interval should be advised in the seronegative pool. In pregnant women with a past history of CMV infection viral titres should be monitored or the foetus be subjected to the serial ultrasound scan scrutiny to ascertain possibility of cCMVi. In prenatal CMV confirmed cases, high dose prolonged valacyclovir therapy has the potential to half the neonatal symptomatic rates in a single study.[11] Hyperimmune globulin therapy has not achieved the desired therapeutic effects in a single study but is currently being evaluated under a trial setting.[12] These treatment options, if ultimately proven efficacious, may force a rethink on the merits of screening for cCMVi.

The limitation with this case report is that CMV PCR on the amniotic fluid, foetal autopsy and tissue analysis may have added weight to diagnosis of cCMVi in this case.

CONCLUSION

Fetal adrenal calcification as a consequence of cCMVi has not been reported in the literature. We report a case of fetal adrenal calcification as a sonographic manifestation of cCMVi in a healthcare worker. cCMVi is common and prevalent especially in populations of lower socioeconomic standing. Certain occupations predispose to this congenital infection which is the most common cause of sensorineural deafness/impairment among newborns. Antiviral therapy after prenatal diagnosis has been shown to lower incidence and severity of this morbidity. Screening of at-risk population such as nursery and healthcare workers should be revisited.

DECLARATION

None.

The patient has granted permission for the scientific reporting and subsequent publication of her experience.

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