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Case Report

Brief Report: 20-Year Follow-Up of an Infant With Neurological Impairment Born to a Mother With Variant Creutzfeldt-Jakob Disease

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Abstract: A term infant born via uncomplicated caesarian section was noted to be jittery, hypotonic, and have pooling of secretions at birth. Over the first four weeks of life, the infant developed four limb hypertonia, hyperreflexia, and clonus. MRI at 3.5 weeks old showed brain immaturity, poor myelination, and increased signal in the dorsal thalami. At six months, dystonic features with decerebrate posturing and jerky limb movements were prominent. Cerebral palsy was diagnosed. Maternal antenatal history revealed six months of psychiatric symptoms and difficulties with ambulation, weakness, and sensory deficits in the first trimester of pregnancy. A diagnosis of new-variant Creutzfeldt-Jakob Disease (vCJD) was confirmed following tonsil biopsy demonstrating pathogenic prion protein deposition in lymphoid follicles on immunohistochemistry and type 4t prion protein on immunoblot. There was continued deterioration with maternal death at 17 months following symptom onset, at which time her infant was six months of age. The infant, now a young adult, has been followed for two decades with static neurological findings. Pathogenic prion proteins have not been isolated in the offspring in multiple tissue biopsies. As little is known about the natural history of in-utero vCJD exposure, long-term clinical vigilance continues.

Keywords: Congenital Infections, Prion, Creutzfeldt-Jakob Disease

Background

Prion proteins (PrP) are matter that lacks nucleic acids, their function is yet to be fully elucidated (Prusiner, 1982). In 1996, cases of a new variant of Creutzfeldt-Jakob disease (vCJD) were linked to bovine spongiform encephalopathy (BSE) in the UK (Collinge and Rossor, 1996). vCJD differed from typical cases of sporadic Creutzfeldt-Jakob disease in that cases presented in younger patients and with more protracted illness progression (mean onset 29 years old) (Barbot *et al*., 2010; Heath *et al*., 2011; Zeidler *et al*., 1997). Whereas in sporadic and iatrogenic cases, misfolded prion proteins (PrPSC) are isolated to neural tissue (Glatzel *et al*., 2003), in cases of vCJD, PrPSC can be found in lymphoreticular (Wadsworth *et al*., 2001) and reproductive tissue (Notari *et al*., 2010; Tamai *et al*., 1992) with evidence of transmission via blood transfusion (Turner and Ludlam, 2009).

Probable vertical transmission of vCJD has been described in animals (Aldhous, 1990; Bencsik *et al*., 2009; Foster *et al*., 2013; Nalls *et al*., 2013), however, there is a knowledge gap in the setting of human prion disease. Given the younger age of onset in persons with vCJD, most of reproductive age, and with extra-neural isolation of PrPSC, vertical transmission has been postulated. Whilst the pathogenesis and biological plausibility are more uncertain relative to other infectious agents that readily cross the maternal-fetal interface (i.e., cytomegalovirus, toxoplasmosis, rubella), vertical transmission of vCJD has potential grave public health implications even decades after birth.

We present the case of a symptomatic infant born to a mother with symptomatic vCJD at the time of birth. Their clinical course has been followed for over two decades.

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Case Presentation

Maternal History

Difficulty walking, leg, and right-sided facial weakness were first noted at 13 weeks gestation. There was a concurrent six-month history of psychiatric symptoms preceding the onset of neurologic symptoms. In the peri-partum period, she had prominent cognitive and memory decline, confusion, and confabulation. Three months postnatally, she was dysarthric, and ataxic and had developed chorea, showing bilateral lower limb pyramidal signs and right-sided-sensory disturbance. Neurological deterioration continued with maternal death 17 months following symptom onset, at which time her infant was six months old.

Maternal Investigations

Neuropsychological testing showed a decreased IQ, memory deficits, and frontal lobe dysfunction. MRI demonstrated high T2-signal in the pulvinar region whilst CSF analysis had raised levels of S100b and 14-3-3 protein Fig. (1). Diagnosis of vCJD was confirmed following a tonsil biopsy taken three months postnatally demonstrating PrPSC deposition in lymphoid follicles on immunohistochemistry and type 4t prion protein on immunoblot. Genomic sequencing of the prion protein gene (PRNP) to identify possible mutations known to be causative for human prion disease was performed, revealing a homozygous mutation (methionine at codon 129).

Post-mortem brain examination demonstrated histologic changes consistent with vCJD: neuronal loss, vacuolation, gliosis, and florid PrPSC plaques. The spinal cord revealed granular PrPSC deposition in the anterior and posterior horns with mild neuronal loss and gliosis. Immunohistochemistry detected PrPSC deposition in the pituitary, spleen, ileum, optic nerve/retina, tonsil, and lymph node. There were no detectable prions in the uterus or ovaries. Unfortunately, the placenta was not examined for PrPSC.

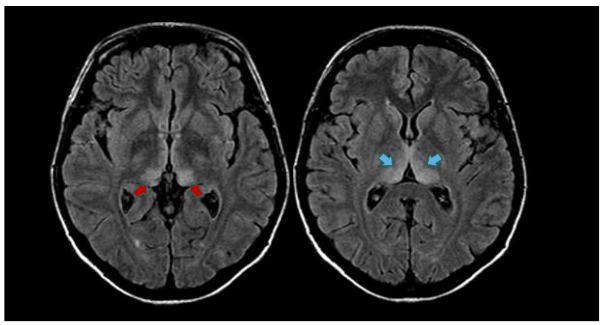

Fig. 1: MRI brain of maternal representative case of variant CJD; Axial FLAIR images at the level of the basal ganglia showing symmetrical pulvinar (red arrows) and dorsomedial thalamic (blue arrows) abnormal bright signal. This combination gives the "hockey stick" appearance

Infant History

The infant was born at 37+6 weeks gestation via uncomplicated elective cesarean section. Parents were non-consanguineous. There were no antenatal toxin/teratogenic exposures and antenatal ultrasounds were normal. Resuscitation was not required at birth. Birth weight was 2.84 kg (25-50%) and head circumference (HC) was 31.5cm (9%). Birth examination revealed: micrognathia, bilateral epicanthic folds, prominent occiput, poorly mobile face, and axial hypotonia.

Within four weeks of age, four-limb hypertonia, hyperreflexia, and clonus developed. At six months, dystonic features with decerebrate posturing and jerky limb movements were prominent. Hypertonia and hyperreflexia persisted with absent suck/swallow and weak cough, left-sided ptosis with poor visual engagement, and an inability to fix and follow. Weight and HC declined to 0.4%. Dystonic movements and limb hypertonia lessened by five years old with decreased fisting. By six years, dystonic posturing was no longer significant. However, there was ongoing axial hypotonia with mild left-sided pyramidal signs and discordant movements. A complete maternal-child clinical timeline can be found in Fig. (2). Weight gain improved to 25-50% by six years old but HC tracked <0.4%.

Now a young adult, severe learning difficulties, bulbar palsy, and epilepsy are present. The patient has no words but can vocalize, having developed 10-15 signs to indicate needs/understanding, and is situationally aware. Examination demonstrates persistent axial and limb hypotonia with brisk deep tendon reflexes and upgoing plantar reflexes. Neurological state remains static.

Infant Investigations

MRI at 3.5 weeks old showed brain immaturity, poor myelination and increased signal in the dorsal thalami consistent with a hypoxic-ischemic injury. Visual acuity, fundi, electroretinogram, and visual evoked potentials were normal and eye movement recordings suggested supranuclear ophthalmoplegia. Serial MRIs done at one, two-and-a-half, five, nine, 12, 14, and 16 years of age established bilateral frontoparietal lobe changes with white matter, fornices, and hippocampal volume loss, and posterior corpus callosum thinning. The pulvinar regions were spared.

Immunohistochemistry examination for PrPSC from lymph node, tonsillar and salivary glands done at various ages over time utilizing ICSM35, KG9, and 12F10 antibodies was negative. Microarray revealed a duplication of the short arm of chromosome (p14.2). The duplication site contained no previously reported pathogenic genes to explain the phenotype and findings were reported as non-contributory. DNA analysis revealed methionine heterozygosity at codon 129 of PRNP.

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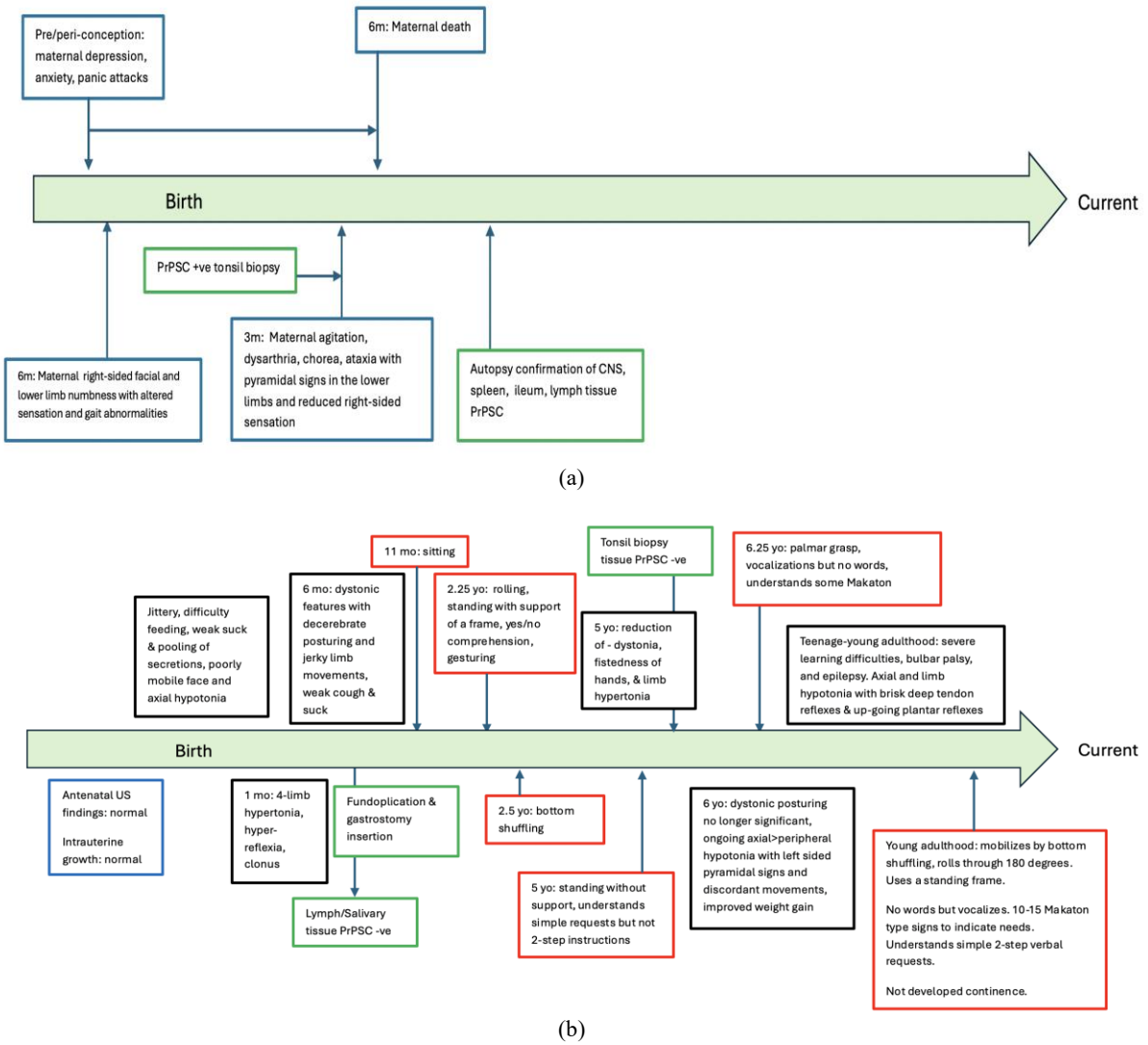

Fig. 2: Clinical timeline of maternal (a) offspring (b) pairing; PrPSC: Misfolded prion proteins (disease-associated): mo: Month old; US: Ultrasound; yo: Year old. Box legend: Black: progeny neurologic findings; Blue: maternal/antenatal findings; Green: surgeries/biopsy; Red: developmental milestones

Discussion

We describe a child, now a young adult, diagnosed with cerebral palsy and global developmental delay exposed in-utero to maternal vCJD. As no alternative cause has been found, it could be postulated that antenatal maternal vCJD may be contributory. Given disease non-progression without definitive evidence of PrPSC, the hypotheses of fetal cerebral insult resulting from maternal vCJD or as a direct consequence of transplacental PrPSC causing prion-induced embryopathy, are both possible. The potential for vertical transmission of vCJD remains conceivable even after two decades and thus clinical monitoring continues.

Several factors support the possibility of human congenital vCJD: (i) vCJD occurs at younger ages, predominantly in reproductive years (Barbot *et al*., 2010) (ii) PrPSC has been isolated in reproductive tissues, umbilical cord leukocytes, and colostrum (Notari *et al*., 2010; Tamai *et al*., 1992) (iii) PrPSC have been detected in mice brains injected with cord blood and placental extracts of women with vCJD (Berrebi et al., 1997) (iv) Prions can now be detected in blood of patients with vCJD and has been shown to be transmitted by blood transfusion, from pre-symptomatic patients (Hewitt *et al*., 2006).

Potential changes in the intrauterine environment contributing to the described patient's phenotype may be explained by high exposure to intrauterine PrPSC

beginning early in gestation. The high degree of exposure throughout the entire gestational period may have overcome the typical "intrauterine sanctuary site". It remains to be answered whether or not prion exposure in-utero can change the biochemical/physiologic intrauterine environment and/or whether PrPSC has direct pathologic effects on the developing fetus.

Several cases of in-utero vCJD exposure have been described. Di Giangi *et al*. (2015) depict a 29-year-old women presenting at 15 weeks gestation with neuropsychiatric symptoms, later diagnosed with vCJD. Born at 24 weeks gestation, the infant succumbed to complications of prematurity. Placental tissue failed to demonstrate abnormalities or PrPSC (Di Gangi *et al*., 2015). The author describes a further six cases, where all infants were asymptomatic at birth. In this case series, 1/5 were found to contain evidence of the pathologic prion isoform in reproductive tissue. Notari *et al.* subsequently verified the presence of prions in the reproductive tissues (uterus/ovary) of a non-pregnant woman with vCJD at autopsy (Notari *et al*., 2010).

An additional case report outlined an 11-month-old female born to a mother deceased of vCJD approximately five months after delivery. The infant presented with dysphagia, convulsions, and hypertonia, although tests for PrPSC in the appendix and lymph tissue of the child were inconclusive. To our knowledge, the placenta and the brain of the child were never examined and vertical transmission was never confirmed. The infant's clinical outcomes were not reported further (Ashraf, 2000). Lastly, Murray *et al*. (2011) present a retrospective review of 125 children born to parents with probable/definitive vCJD (mothers affected 71/125). Seventeen were born within one year of parental disease onset; in eight cases the parent was symptomatic at birth and four were symptomatic at conception. No cases of symptomatic offspring were uncovered in this larger cohort (all <14 years old at publication) (Murray *et al*., 2011).

The absence of definitive evidence of congenital prion disease is multifactorial. Little is known about transmissibility or incubation period in heterozygote genotypes and thus a protracted incubation period in offspring remains possible. Although variability in incubation is understood to be dependent on the mode of transmission (<2 years with CNS tissue, >30 years if infected via peripheral tissues) (Brown *et al*., 2020), little is known when exposed in-utero. Genotypic variance at codon 129 of the prion protein is known to increase host susceptibility to vCJD in a homozygous state, although transmission has been shown in heterozygous patients (Peden *et al*., 2004). Differences in susceptibility based on fetal genetics have also been shown in scrapie-infected ewes (Alverson *et al*., 2006). Timing of infection in pregnancy and mode of delivery may be crucial to transmissibility, but isolation of prions in the reproductive tract and colostrum suggests the possibility of maternal-fetal transmission at any gestational age and/or in the peri-partum period. Infectivity is also potentially dependent on prion blood concentration. Thus, protracted follow-up in infants exposed in-utero is advisable.

Conclusion

To our knowledge, this is the first surviving symptomatic infant exposed to vCJD in-utero. They are one of the few infants exposed to vCJD antenatally to show abnormal neurological signs from birth. There have yet to be any signs/symptoms of disease progression despite two decades of follow-up. PrPSC have not been isolated in the offspring, however, clinical vigilance is required due to the possibility of a long latency period, especially with favorable genetic heterozygosity at codon 129. As little is known about the natural history of in-utero exposure, long-term clinical monitoring continues.

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Author’s Contributions

Justin Penner: Served as the primary author of the manuscript.

Anjali Rampersad: Contributed to clinical data collection, manuscript preparation, and editing.

James E. Burns: Assisted with manuscript preparation and editing.

Diane Smyth: Provided expert clinical insights, assisted with patient management, and reviewed the manuscript.

Hermione Lyall: Offered expert clinical contributions, supervised the drafting and editing of the manuscript, and served as the primary physician for the patient.

Ethics

A full ethics review under the terms of the governance arrangements of research ethics committees in the UK was not required. Consent for publication was provided by the patient’s substitute decision maker.

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