

A Cluster of Anencephaly Cases: The Potential Preventative Role of Folic Acid Fortification

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Abstract

Introduction

There were four cases of severely abnormal fetal cranial views on ultrasound over a two-week period at a peripheral maternity unit. We describe three of these cases with consent.

Cases

All cases were confirmed anencephaly/acrania by fetal medicine at a tertiary referral centre between 12-16-weeks' gestation. In two cases the parents opted for genetic testing. This condition is not compatible with life and this cluster highlights the difficult decisions individuals and couples are faced with.

Outcome

Two of the couples opted for termination under Section 11 of the Health Act 2018. One set of parents chose to continue the pregnancy and had an emergency caesarean section followed by a neonatal death within hours of delivery.

Discussion

Given how rare these conditions are, this cluster gives an opportunity to review an important and largely preventable anomaly. The introduction of folic acid food fortification could majorly contribute to prevention.

Introduction

Acrania anencephaly or acrania- exencephaly- anencephaly sequence is the progression from a normal-appearing exposed brain due to absent cranium (acrania) to an amorphous brain mass (exencephaly) to no recognisable brain tissue (anencephaly).¹ Acrania is the absence of cranial vault and cerebral hemispheres.² Anencephaly falls under the umbrella term of neural

tube defects (NTD). It results from failure of the neural tube to close during fetal development.^{2,3} The neural tube is created as the neural plate folds and fuses. Any interruption to the neural tube closure process can lead to structural abnormalities known as NTDs.^{2,3} Anencephaly refers to one of the two predominant types of NTD that results from 'the failure of closure of the rostral end of the neural tube'.^{2,3,4} Spina bifida is the other predominant NTD which results from failure of caudal end closure.² Anencephaly is believed to be a multifactorial process with environmental and nutritional elements playing a considerable role.^{2,3}

At 12 weeks' gestation it can be suspected by the absence of a normally ossified skull and exencephaly (distortion of the brain).⁵ After 16 weeks' gestation, ultrasound will show anencephaly whereby the brain is destroyed.² This occurs in approximately 1 in 1000 pregnancies at 12 weeks' gestation.⁵ Considering this, to identify 4 cases of anencephaly in quick succession is a rarity. It is not common to identify chromosomal defects in isolated acrania. Other central nervous system defects are identified in approximately 50% of cases.⁵ Spina bifida is evident in a quarter of cases of acrania.⁵

Case 1

A 37-year-old primip at her dating scan at 12+6 weeks gestation the crown rump length (CRL) was satisfactory but the biparietal diameter (BPD) was below the expected normal range. A second opinion at the tertiary fetal medicine unit confirmed an abnormal fetal head, a visible mandible, absent orbits, and no definite skull bones above the mandible. There was bilateral talipes. The hands were open but fixed and flexed. Cardiac assessment revealed an abnormal four chamber view. Following counselling a repeat scan at 13+ weeks' gestation showed acrania and kyphoscoliosis and a chorionic villus sample (CVS) was performed with no genetic cause for the abnormality identified.

The case was discussed at tertiary Fetal Medicine Multi-Disciplinary Team (MDT) meeting, and it was agreed the couple could proceed with TOP under Section 11. Compassionate TOP took place; vaginal delivery ensued with no complications.

Case 2

A 36-year-old lady with a history of two previous caesarean sections and one partial molar had a reported normal dating scan at 12 weeks' gestation. At 16 weeks' gestation she was referred from a private scan with a suspicion for anencephaly. A departmental scan at 16+2 weeks gestation revealed an abdominal circumference on the 24th centile and a femur length

on the 31st centile but evidence of anencephaly; the skull was not visible, and the BPD could not be measured.

Repeat scan at a tertiary fetal medicine unit at 16+5 weeks gestation confirmed anencephaly with absence of the cranial vault and cerebral hemispheres. The patient was counselled regarding a poor prognosis. Multi-disciplinary discussion took place and the patient opted for compassionate termination with induction of labour (IOL). A female fetus with no unbalanced genetic abnormality was delivered via vaginal delivery following IOL at 18 weeks' gestation.

Case 3

A 33-year-old P2 (2 previous vaginal deliveries) with a BMI of 33 presented for a dating scan at 16 weeks +2 days gestation. There were appearances of anencephaly and referral for fetal medicine was made. Tertiary fetal medicine scanning confirmed the finding of anencephaly. Amniocentesis was offered and performed with no adverse event. The result was a normal array. The couple chose to continue the pregnancy and at 38 weeks' gestation in she presented in early labour. There was malposition; oblique cephalic and it was deemed to be unsafe to proceed with labour in the context of anencephaly. A category II caesarean section was performed with no adverse outcomes. A male baby was born alive weighing 2940g. Comfort care was given; the baby died at 3 hours of life.

Discussion

Nutritional and environmental factors play a role in the pathogenesis of anencephaly.^{2,3} Deficiencies of folate have been repeatedly linked to NTD development. Folate is a coenzyme involved in purine and pyrimidine synthesis and in methylation.² Folate deficiency can be a result of the following: 1) insufficient dietary intake of folate, 2) increased demand for folate, 3) folate malabsorption, and 4) drugs that block/interrupt folate absorption.² The use of folate periconceptually varied amongst the three cases in this cluster; one patient was taking folic acid preconceptually, one patient was unsure of the timing of her folic acid intake, and one patient did not take any folic acid periconceptually. Approximately 40% of pregnancies in Europe are unplanned and so many have not taken prophylactic folic acid.⁷ This lack of consistent folic acid consumption underpins the need for folate fortification on a national level in Ireland and internationally.

We know folic Acid supplementation can prevent NTDs.⁸ A randomised control trial (RCT) by the UK Medical Research Council (MRC) demonstrated that administration of 4.0mg FA every day until 12 weeks' gestation prevented 72% of NTD recurrences.^{8,9} This finding was further

supported by Hungarian research showing 0.8mg FA daily in over 4,000 women planning pregnancy significantly reduced NTDS in those taking FA compared to those in the control group.¹⁰ In Ireland, 400mcg folic acid was recommended prior to conception and during the first 12 weeks of pregnancy from 1993 onwards.⁸

Prevention of NTDs by increasing maternal folate levels involves increasing dietary intake, supplementation of FA and food fortification with FA. Impacts on dietary habits have had limited success.^{8,11} Despite international advice on periconceptual FA, NTD prevalence has remained static in most countries.^{8,12} This is likely due to the unplanned nature of up to half of all pregnancies, FA supplementation prior to the closure of the neural tube is less than it should be.^{7,8,12} Mandatory FA food fortification has proven successful internationally. In 2007, a large Canadian study revealed that NTD incidence had reduced from 1.58 per 1,000 births pre-fortification to 0.86 per 1,000 births post mandatory fortification.^{13,14} Spina bifida had the greatest reduction of 53% whilst anencephaly cases were reduced by 38%.^{13,14} In the United States, folic acid fortification is considered 'one of the most successful public health initiatives'.^{15,16} Since 1998, NTDs have been reduced by 19-32% since FA fortification was introduced in the US.¹⁵ Other countries with successful reductions in NTD include South Africa, Costa Rica, Chile, Argentina, and Brazil with figures ranging from 19-55% since introduction of FA food fortification.¹⁵

The ongoing national policy of voluntary FA food fortification has not garnered success and as per the Food Safety Authority of Ireland recommendations in 2006 and 2016, mandatory fortification needs be implemented.⁸ In September 2021, the UK announced a mandate that starch will be fortified with FA¹⁷ and from 2026 fortification of non-wholemeal wheat flour will be mandated. Leading UK expert in this field Professor Nicholas Wald argues that fortification of all flour and rice as well as raising the fortification level could prevent up to 80% of NTDs instead of only 20% with the UK's current policy.¹⁸

Although fortification can reduce NTD incidence, there are other contributing factors that should be addressed including medications, diabetes, temperature regulation, and Vitamin A. Neural tube defects can be caused by anti-epileptic drugs (AEDs). Examples of these include Carbamazepine, Phenytoin, and valproate which alter absorption of folate ultimately leading to a reduction in blood levels.² Of the three AEDs, valproate is the most teratogenic.^{2,19} Trimethoprim and Aspirin are two relatively common drugs also known to be folic acid antagonists.^{2,19} There was no history of AEDs in our cluster.

Maternal diabetes can complicate pregnancies and increase the risk of birth defects.² Physiologically, high blood glucose levels alter organogenesis.^{2,20} Hyperthermia has also been identified as impacting 'anterior neural tube closure' and correlation with anencephaly has been noted.² Exposure to saunas, febrile illness, and exercising in high temperature

climates.^{2,21} High levels of Vitamin A are known to be teratogenic and prevent closure of the anterior neural tube, leading to anencephaly and other NTDs.^{2,22} Of note, no patients in this cluster reported any history of diabetes, hyperthermia, or vitamin A exposure.

Compatibility with life is not a possibility for anencephaly. Prevention is the mainstay of managing this condition and the most effective way is to recommend those of childbearing age take folic acid daily. This is especially relevant for those on anti-epileptic drugs and preconceptual counselling is vital for these patients. Diagnosis of anencephaly is via ultrasound and additional maternal serum levels can aid diagnosis. Termination of pregnancy is an option when anencephaly is diagnosed.²

In conclusion, there were four cases of anencephaly diagnosed within a two-week timeframe at a peripheral unit. Given how rare this NTD is, the cluster occurrence of these cases gives an opportunity to review anencephaly as well as highlight the need for prevention of NTD. Evidence for successful reduction of NTD with food fortification has been demonstrated internationally and the need for this in Ireland is evident from this cluster of cases.

Abbreviations:

CRL: Crown Rump Length

BPD: Biparietal Diameter

CVS: Chorionic Villus Sample

MDT: Multi-Disciplinary Team

IOL: Induction of Labour

SVD: Spontaneous Vaginal Delivery

EFW: Estimated Fetal Weight

HC: Head Circumference

PCR: Polymerase Chain Reaction

CSF: Cerebrospinal Fluid

MRI: Magnetic Resonance Imaging

Declarations of Conflicts of Interest:

None declared.

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