

Prenatal Diagnosis of Lissencephaly Associated with Biallelic Pathologic Variants in the *COQ2* Gene

Diagnóstico Pré-natal de Lisencefalia Associada a Variante Bialélica Patológica do Gene *COQ2*

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ABSTRACT

Primary CoQ10 deficiency comprises several clinical phenotypes. Nevertheless, there are no reports so far of lissencephaly linked to CoQ10 deficiency. Lissencephaly is a developmental condition associated with defective neuronal migration which may be depicted on fetal neurosonography by persistence of a laminar pattern beyond 34 weeks and abnormal cortical sulcation. We report an index case of a male fetus diagnosed with abnormal lamination, characterized by the persistence of a laminar pattern during late pregnancy, following a normal second trimester scan. Post-natal whole exome sequencing revealed biallelic pathologic variants in the *COQ2* gene which encodes an enzyme that is part of coenzyme Q10 (COQ10 or ubiquinone) pathway and is involved in the biosynthesis of CoQ, a redox carrier in the mitochondrial respiratory chain and a lipid-soluble antioxidant. This case underscores the heterogeneity of the prenatal phenotypic presentation of pathogenic variants in the *COQ2*, namely lissencephaly.

Keywords: Lissencephaly/genetics; Malformations of Cortical Development; Mutation/genetics; Prenatal Diagnosis; Ubiquinone

RESUMO

A deficiência primária de CoQ10 traduz-se numa variedade de fenótipos clínicos. Todavia, não existe até à data nenhuma descrição deste défice associado a lisencefalia. A lisencefalia consiste numa alteração do desenvolvimento cortical cerebral em que se verifica um defeito na migração neuronal, detetável na neurosonografia pela persistência de um padrão de laminação cerebral após as 34 semanas de gestação e por alterações nas circunvoluções corticais. Neste trabalho descreve-se o caso de um feto masculino com um padrão de laminação cerebral alterado, detetado na avaliação ecográfica do terceiro trimestre, após exame morfológico sem alterações. A sequenciação pós-natal do exoma revelou uma variante bialélica patológica do gene *COQ2*, que codifica uma enzima da via da coenzima Q10 (COQ10 ou ubiquinona), envolvida na biossíntese do CoQ, um transportador *redox* da cadeia respiratória mitocondrial e anti-oxidante lipossolúvel. Com este caso, destaca-se a heterogeneidade fenotípica pré-natal das variantes patogénicas no gene *COQ2*.

Palavras-chave: Diagnóstico Prenatal; Lisencefalia; Mutações/genética; Perturbações da Migração Neuronal; Ubiquinona

INTRODUCTION

Coenzyme Q10 is both an antioxidant and an integral part of the mitochondrial respiratory chain, where it acts as an electron acceptor. Primary CoQ10 deficiency comprises several clinical phenotypes. Nevertheless, until now there is no description of lissencephaly linked to CoQ10 deficiency. Lissencephaly (LIS) is a developmental condition associated with defective neuronal migration which may be depicted on neurosonography (an ultrasound of the brain and central nervous system) by persistence of a laminar pattern (due to the layer arrangement of brain) beyond 34 weeks and abnormal cortical sulcation. We report an index case of a male fetus diagnosed with abnormal lamination during late pregnancy following a normal second trimester scan.

CASE REPORT

A 38-year-old woman, *grávida 2 para 1*, without any medical condition or known exposure to teratogens, family history of congenital disease or consanguinity, was referred to our unit at 32 weeks of gestation because of fetal growth

restriction (FGR) and oligohydramnios. She had been diagnosed with gestational diabetes at 12 weeks of gestation. An amniocentesis was indicated because of first trimester combined screening (with normal ultrasound markers) suggesting high risk of trisomy 13 and 18, and the karyotype was normal for a male fetus. There were no fetal abnormalities found on detailed second trimester ultrasound.

At week 32, even though the estimated fetal weight was on the first centile and the Doppler evaluation of the umbilical artery was normal, the cerebroplacental ratio was decreased (favoring the occurrence of redistribution of cardiac output to the cerebral territory).

Transvaginal neurosonography was performed at 34 weeks of gestation. An increased echogenicity of the periventricular area and a clear persistence of a laminar pattern (Fig. 1) were depicted. As severe oligohydramnios was present, a cordocentesis was carried out to check for cytomegalovirus infection (CMV-polymerase chain reaction) and comparative genomic hybridization array (CGH-array) was

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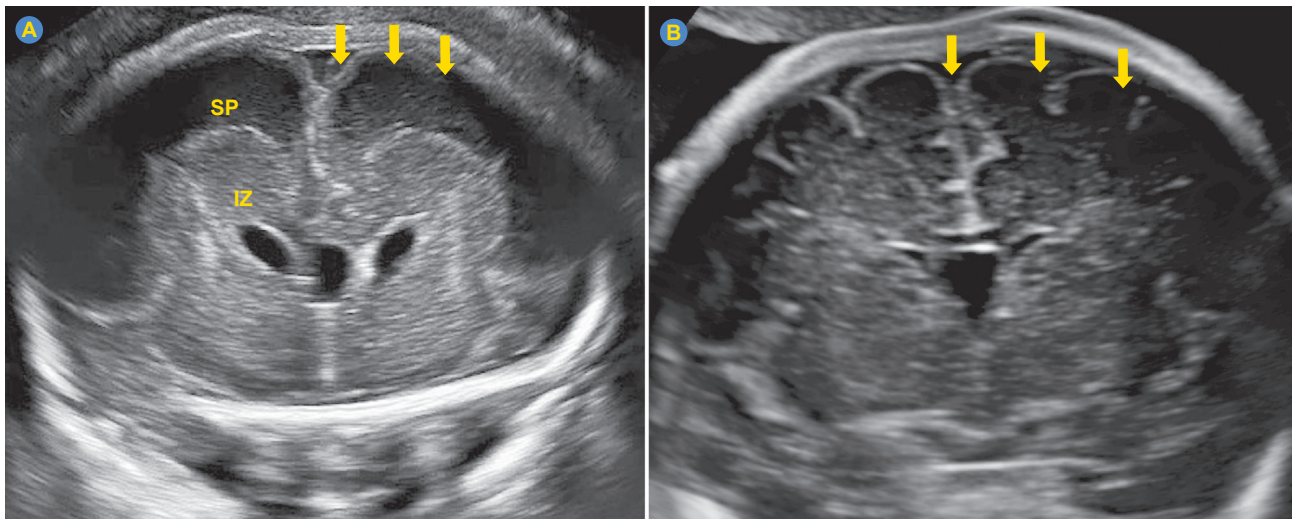


Figure 1 – (A): image of transvaginal neurosonography performed in the current case, at 34 weeks of gestation. Coronal section image of the fetal's brain, where the intermediate zone (IZ) and the subplate zone (SP) are easily identifiable. This image shows a clear persistence of a laminar pattern, which is anomalous at this gestational age. (B): a transvaginal neurosonography performed at 33 weeks of gestation in a normal fetus. Coronal section image of brain with no evidence of separate subplate and intermediate zones. The arrows show normal sulcation of the brain on the right, and its absence on the left.

performed, both with normal results. The bladder remained empty in all tests performed at our institution. Hyperechogenic kidneys were evident at 35 weeks, with normal male genitalia. In subsequent ultrasound scans the increased echogenicity of the intermediate zone was evident as well as an abnormally prominent laminar pattern (Fig. 2).

Induction of labour was carried out at 38 weeks of gestation. A male fetus was delivered vaginally, weighing 1700 g, with an Apgar score of 5/7/7 and the outcome was neonatal death at 25 minutes of life. The newborn had several dysmorphic features, namely high nasal bridge, micrognathia (an undersized lower jaw) dysmorphic ears, nail hypoplasia and talipes equinovarus of the left foot (also known as club-foot, a congenital deformity in which one or both feet are

excessively plantar flexed, with the forefoot swung medially and the sole facing inward).

The neonatal autopsy confirmed the diagnosis of lissencephaly and showed hypoplastic corpus callosum. Post mortem whole-exome sequencing revealed the presence of two compound heterozygous variants in the *COQ2* gene: c.590G>A p.(Arg197His) (classified as likely pathogenic) and c.827del p.(Gly276Valfs*20) (classified as pathogenic).

Biallelic pathogenic variants in the *COQ2* gene are associated with primary coenzyme Q10 deficiency type 1, which is a rare, clinically heterogeneous autosomal recessive disorder. Both parents are asymptomatic carriers of one clinically relevant variant in *COQ2* and are not at risk of developing symptoms. However, in future pregnancies, this

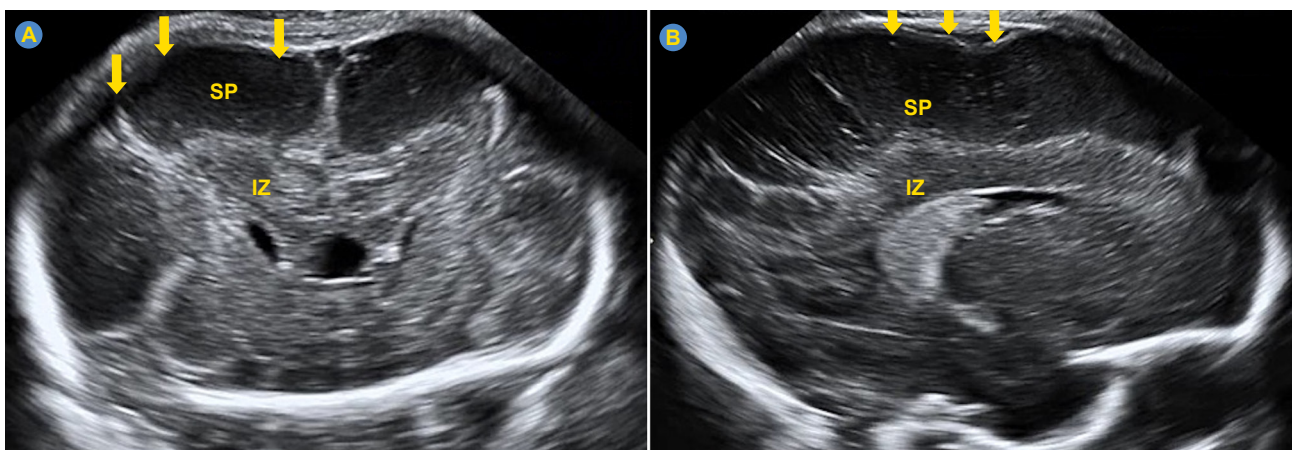


Figure 2 – Image of coronal (A) and para-sagittal (B) section of the fetal brain, at 37 weeks. There is an increased echogenicity of the intermediate zone and late persistence of the abnormal laminar pattern. Sulcation (arrows) continues to be absent at this gestational age.

IZ: intermediate zone; SP: subplate zone.

couple has a 25% risk of having an affected child.

Genetic counselling was offered to the couple, including discussion of their reproductive options. A subsequent pregnancy was achieved and invasive prenatal diagnosis in a subsequent pregnancy and the genetic test confirmed that the fetus was not affected. After an uneventful pregnancy, a healthy male newborn was delivered vaginally at term.

DISCUSSION

We described the prenatal ultrasound findings of a case of biallelic pathogenic variants in *COQ2* linked to primary coenzyme Q10 deficiency type 1. In our case, the combination of these variants in the compound heterozygous state primarily presented prenatally as severe fetal growth restriction (FGR), abnormal kidney function and lissencephaly. There are previous reports in the literature of the clinical presentation of *COQ2* deficiency.^{1,2} The clinical spectrum may vary from severe multiple organ dysfunction to nephrotic syndrome with or without neurological manifestations, and later milder presentations of multi system atrophy and retinitis pigmentosa. Nevertheless, a prenatal clinical description of this condition associated with lissencephaly has not been previously published and it may be taken into consideration when FGR, renal impairment and abnormal brain lamination pattern are depicted prenatally. Furthermore, with the recent possibility of whole exome sequencing (WES) and improved accuracy of fetal brain imaging, a growing number of LIS-associated genes have been identified.^{3,4}

Lissencephaly is a malformation of the cortical development associated with developmental delay, intellectual impairment, and seizures.⁵ It has been associated with defective neuronal cell migration which results in abnormal cerebral convolutions. Normal cortical sulci and gyri development relies on the proliferation of neuroblasts in the germinal matrix, its migration to the cortical surface and arrangement within the maturing cerebral cortex.⁶ Gyration and sulcation occur mostly after 32 weeks of gestation, which usually corresponds to migration ending. Typical fetal transient cerebral lamination has been demonstrated on histology, in magnetic resonance imaging and in ultrasound scan.⁷ Transient fetal laminar brain areas include the ventricular zone (VZ), the intermediate zone (IZ), the subplate zone (SP) and the cortical plate (CP). As described by Pugash *et al*,⁷ the cortical plate is anechoic and identical to the underlying subplate zone before 28 weeks of gestation; the intermediate zone is more echogenic than the subplate and the limit between them is always visible. The ventricular zone has higher echogenicity and surrounds the lateral ventricles. After 28 weeks, the interface between the IZ and the SP is unclear and beyond 33 weeks of gestation there is no evidence of separate subplate and intermediate

zones, and the subcortical brain appeared homogeneous. On a retrospective study with 68 fetuses with abnormal cerebral lamination for gestational age, the persistence of a brain laminar pattern on ultrasound beyond 33 weeks was associated with type 1 lissencephaly or cytomegalovirus infection.⁷

Type 1 lissencephaly can be isolated or associated with various phenotypes such as Miller-Dieker syndrome or Norman-Roberts syndrome.⁸ Coenzyme Q10 (CoQ10 or ubiquinone) is a lipid-soluble component of the mitochondrial respiratory chain and its primary deficiency comprises several clinical phenotypes, such as encephalomyopathy, severe infantile multisystemic disease, cerebellar ataxia, isolated myopathy, or nephrotic syndrome.⁹

This case highlights the importance of whole exome sequencing for the improvement of our knowledge in prenatal diagnosis, since it was that genetic test that provided clinically relevant information for this couple's counseling regarding further pregnancies. To the best of our knowledge, this is the first description of lissencephaly diagnosed prenatally associated with biallelic pathologic variants in the *COQ2* gene.

AUTHOR CONTRIBUTIONS

RRS: Study design, data collection, conception of the manuscript.

MR: Study design, data collection, critical review.

TL: Study design, data collection, conception of the manuscript, critical review.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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