U.PORTO

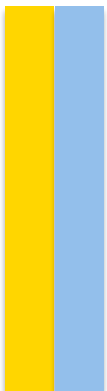
MESTRADO INTEGRADO EM MEDICINA
OBSTETRÍCIA

Congenital disorders of the corpus callosum and development during postnatal life: A case report and review of the literature

Mafalda Taveira da Fonseca Barreira Calheiros

M

2022



Congenital disorders of the corpus callosum and development during postnatal life: A case report and review of the literature

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Estudante: Mafalda Taveira da Fonseca Barreira Calheiros

6º ano Mestrado Integrado em Medicina

Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Rua de Jorge Viterbo Ferreira nº228, 4050-313 Porto

Endereço eletrónico: mafaldacalheiross@gmail.com

Orientador: Prof. Doutora Maria Isabel Ribeiro de Carvalho e Sá Monteiro

Assistente Hospitalar Graduado de Ginecologia e Obstetrícia – Centro Hospitalar Universitário do Porto

Colaboradora Externa do Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Coorientador: Prof. Doutor Luis Guedes Martins

Assistente Hospitalar Graduado de Ginecologia e Obstetrícia – Centro Hospitalar Universitário do Porto

Professor Associado Convidado do Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Maio de 2022

Porto, Junho de 2022

Estudante: Mafalda Taveira da Fonseca Barreira Calheiros

Mafalda Calheiros

Orientador: Prof. Doutora Maria Isabel Ribeiro de Carvalho e Sá Monteiro

Maria Isabel Sá

Coorientador: Prof. Doutor Luis Guedes Martins

Agradecimentos

Gostaria de agradecer à minha orientadora e coorientador, Dra. Isabel Sá e Professor Doutor Luís Guedes Martins a orientação, auxílio na escolha do tema, e revisão de conteúdos desta dissertação.

Ao Instituto de Ciências Biomédicas Abel Salazar e aos professores por terem feito parte da minha formação.

Ao meu pai, à minha mãe, à minha irmã, à minha família e amigos por serem os meus pilares, cada um à sua maneira.

Resumo

Introdução: Esta dissertação tem como objetivo descrever um caso clínico de uma grávida que apresenta um feto com agenesia completa do corpo caloso.

Métodos: A descrição do caso clínico baseou-se na análise do processo clínico eletrônico das doentes em questão, presentes no sistema informatizado SClínico®. A revisão teórica foi baseada em artigos encontrados na plataforma Pubmed®.

Caso Clínico: Descrevemos o caso de uma grávida de 28 anos que se apresentou no nosso serviço no terceiro trimestre com um feto com aparente agenesia completa do corpo caloso.

Na vida pós-natal e na primeira infância, a criança teve crescimento e desenvolvimento normais. Aos 10 anos a criança volta para consulta de neurodesenvolvimento, por dificuldades de aprendizagem, deficit de atenção e hiperatividade, e distúrbios do sono. Foi medicada com melatonina e metilfenidato 30mg.

Discussão: A agenesia do corpo caloso é uma doença congênita caracterizada por a sua ausência parcial ou completa. Pode se apresentar como isolada ou associada a outras anomalias congénitas extra ou intracranianas. O diagnóstico pode ser feito por ultrassonografia no segundo trimestre da gravidez. As consequências cognitivas, comportamentais e neurológicas da agenesia do corpo caloso são amplas, sendo o prognóstico desfavorável quando esta anomalia ocorre em associação com alterações genéticas ou no contexto de síndrome polimalformativo. Quando isolada, o curso assintomático da doença é comum, porém, mesmo em doentes sem déficits aparentes, podem ocorrer alterações neuro psicológicas subtis na idade adulta.

Conclusão: O prognóstico da agenesia do corpo caloso é incerto devido à variabilidade de manifestações neurocognitivas que os achados neuroanatómicos não podem prever, sobretudo na sua forma aparentemente isolada. Isso pode levar à identificação tardia de alterações neurocognitivas e ao estabelecimento tardio de estratégias de reabilitação. Portanto, indivíduos com agenesia completa do corpo caloso requerem acompanhamento neurocognitivo contínuo, apesar de terem função cognitiva normal durante a infância.

Palavras-chave: Agenesia do corpo caloso, Desenvolvimento neurocognitivo, Prognóstico

Abstracts

Background: This dissertation aims to describe a clinical case of a pregnant woman who presents with complete agenesis of the corpus callosum.

Methods: The clinical case description was based on the analysis of the clinical records of the electronic clinical process of the patient's clinical files (obstetrics and paediatrics), present in the *SClínico*® computer system. The theoretical review was based on articles found on the *Pubmed*® platform.

Case Presentation: We describe the case of a 28-year-old pregnant woman who presented to our department on the third trimester with a fetus with an apparent complete corpus callosum agenesis.

In postnatal life and early childhood, the infant had normal growth and development. At 10 years old the child comes back for a neurodevelopment appointment, with complaints of learning difficulties, attention deficit hyperactivity disorder and sleep disturbance. She was medicated with melatonin and methylphenidate 30mg.

Theoretical Review: Agenesis of the corpus callosum is a congenital cerebral malformation characterized by its partial or complete absence. It can be isolated or as part of a complex congenital syndrome. The diagnosis can be made by ultrasound in the second trimester of pregnancy. The cognitive, behavioural, and neurological consequences of corpus callosum agenesis are wide-ranging, and the prognosis is unfavorable when this anomaly occurs in association with genetic alterations or in the context of a polymalformative syndrome. When isolated, the asymptomatic course of the disease is common, however, even in patients without apparent deficits, subtle neuropsychological changes can occur in adulthood.

Conclusion: Prognosis in agenesis of the corpus callosum is uncertain due to the variation in neurodevelopmental outcomes that neuroanatomic findings cannot predict. This can lead to late identification of neurocognitive alterations and delayed establishment of rehabilitative strategies. Therefore, patients with this condition require close neurocognitive follow-up despite having normal cognitive function during childhood.

Keywords: Agenesis of the corpus callosum, Neurocognitive development, Follow-up

Abbreviations and acronyms

ADHD – Attention deficit and hyperactivity disorder

AgCC – Corpus Callosum Agenesis

CC – Corpus Callosum

CMA - Chromosomal Microarray Analysis

CNS - Central Nervous System

CSP - Cavum Septi Pellucid

MRI - Magnetic Resonance Imaging

US – Ultrasound

Index

1. Introduction.....1

2. Objectives.....2

3. Methodology.....2

4. Ethics.....2

5. Case Presentation.....2

6. Corpus Callosum.....8

7. Corpus callosum defects.....9

8. Neuroimaging.....9

9. Associated Abnormalities.....12

10. Prenatal screening, Counselling and Prognosis.....12

11. Post-natal development of this pathology.....13

12. Conclusion.....15

13. Bibliography.....22

List of Figures

Figure 1 - Conners' Teacher Rating Scale 17
Figure 2 - Conners' Parent Rating Scale 19
Figure 3 - Swanson, Nolan and Pelham Teacher and Parent (SNAP) Rating Scale-IV Rating Scale - Teacher 20

1. Introduction

The central nervous system (CNS) is responsible for the interpretation and transmission of sensory, cognitive, and motor information. The corpus callosum (CC) is a structure composed of transverse fibers which transmit information between the cerebral hemispheres. The corpus callosum starts to develop from 8 weeks onwards, developing from front to back. Agenesis of corpus callosum (AgCC) is a congenital disorder characterized by its partial or complete absence. It can be isolated or associated with other congenital extra or intracranial abnormalities. The prevalence in the general population varies depending on the sources, the usual range being 1:5000 to 1:4000. [1]

The cause of agenesis of the corpus callosum is usually not known. It can be primary or may be associated with chromosomal disorders (trisomy 18, 13, 8), genetic syndromes or result from a secondary destructive lesion or teratogens, such as alcohol, sodium valproate or cocaine.

The diagnosis can be made by ultrasound (US) in the second trimester of pregnancy. However, it is difficult as the CC is not seen in the usual axial sections of the fetal head, but its agenesis can be suspected in the presence of indirect signs, such as the absence of the cavum septi pellucid (CSP) and ventriculomegaly. AgCC is demonstrated with coronal and sagittal sections of the fetal head, using multiplanar imaging. In this situation, magnetic resonance imaging (MRI) should be performed to investigate associated anomalies, namely neuronal migration disorders and heterotopias.

The cognitive, behavioural, and neurological consequences of AgCC are wide-ranging. The most prevalent clinical implications reported in symptomatic patients are epilepsy, motor impairment and intellectual disability. Nevertheless, an asymptomatic course of the disease is common, and the disorder can have no apparent symptoms in the mildest cases for many years. Subsequently, intelligence may be only slightly impaired and subtle psychosocial symptoms may be present. The associated diseases can add other clinical characteristics.

In the presence of aneuploidies or other intra or extra-cranial anomalies, the prognosis is poor. In isolated agenesis, the prognosis is better, with normal development in most cases. However, parents should be informed that in apparently isolated corpus callosum agenesis, about 15% of cases will have other anomalies not identified in fetal life.

The main objective of the present work is a literature review based on a case report of an isolated AgCC.

2. Objectives

This dissertation aims to review the existing bibliography on defects of the corpus callosum, illustrated with a case report. The most current information was selected, systematising knowledge so far, emphasising the different types of corpus callosum defects, embryology, image findings, associated abnormalities, prenatal diagnosis, and post-natal development of this pathology. Patients with this disorder require a strict follow-up during their prenatal and postnatal life. Thus, it is intended to highlight the importance of a long-term follow-up to improve physicians' approach to this cerebral malformation.

3. Methodology

The methodology of this work was through the selection and weighted analysis of research articles and bibliographic review. Scientific articles were searched through the PubMed platform, and the main search concept was to combine "corpus callosum agenesis" with the related terms, such as "etiology", "neurodevelopment", "diagnosis", "follow-up" and "prognosis" published in English and Portuguese in the last ten years.

The collection of information related to the patient's clinical files (obstetrics and paediatrics) from the Department of Women and Reproductive Medicine of CHUPorto followed the necessary compliance and consent.

4. Ethics

The study was approved by the hospital's Ethics Committee of CHUPorto with the reference number 2021.335 (CC-DEFI/288-CE). Written informed consent was obtained from the patient.

5. Case Presentation

We describe the case of a 28-year-old pregnant woman who presented to our department on the third trimester.

The patient is a healthy, pregnant woman that has the 6th grade, works as a seamstress and has a history of learning disabilities. The other parent has the 6th grade, works as an administrator of a multifunctional company, has hypertension and hypercholesterolemia. There is no other relevant

family history. They are both non-smokers. The family is nuclear, and the environment at home is not disruptive.

In her past, there was a first gestation with placental abruption at 30 weeks of gestation with fetal death. The anatomopathological examination revealed a “male fetus, with weight and biometric parameters, corresponding to an approximate gestation of 30 weeks. Placenta with large retroplacental hematoma, subacute and older infarctions involving 15% of the placental volume, deciduoid vasculopathy; thrombotic and proliferative fetal vasculopathy.”

She was monitored in preconception counselling. MTHFR gene mutation test was performed, and a mutation c.1298A>C (p.E429A) was detected in heterozygosity. The result alone is not enough to confirm a thrombophilia. Also, anti-cardiolipin antibodies, anti-ß2 glycoprotein antibodies and homocysteine were negative, therefore, an antiphospholipid syndrome was excluded.

Due to her obstetric past, she was considered a high-risk pregnancy. She took progesterone, magnesium, folic acid and doxylamine succinate-pyridoxine hydrochloride since the first trimester. Additionally, she started thromboprophylaxis with enoxaparin (40mg/0.4ml) once daily via subcutaneous injection and acetylsalicylic acid 100mg orally once a day until 35 weeks of gestation.

The first trimester and second-trimester screening tests were normal. The first and second trimesters’ blood test results were negative for VDRL, no immunity to toxoplasmosis, immunity to rubella, immunity to cytomegalovirus and negative for hepatitis B, C and HIV.

In the third trimester, she was referred to our department. On the US at a gestational age of 30 weeks + 3 days there was dilation of the cerebral ventricles with larger diameters of 18.7 and 19.8 mm with a likely diagnosis of AgCC with no other morphological changes detected. Third-trimester blood tests were made at a gestational age of 30 weeks + 3 days, with normal ferritin, low T4 0.8ng/dL, normal TSH 0.97, no immunity to toxoplasmosis and immunity to cytomegalovirus. The mother denied ingestion or consumption of drugs, tobacco, alcohol, or other drugs during pregnancy. An MRI and an invasive prenatal test were recommended and an indication for a new US examination between 33 weeks was made. The patient did not want to perform invasive prenatal diagnostic tests due to the associated risks.

MRI report at 30 weeks + 5 days described complete agenesis of the corpus callosum, with colpocephalic elongation of the lateral ventricles, measuring approximately 19 mm on the right and

16 mm on the left, without tension and alteration of the sign of the adjacent parenchyma. It was considered isolated agenesis, with no associated interhemispheric cyst or suspicious images of cerebellar malformations, cortical dysplasia or other midline defects.

Ultrasonography at 33 weeks + 0 days showed bilateral dilatation of the cerebral ventricles, the largest with 23 mm and the other with 20 mm. Ultrasonography at 35 weeks + 6 days showed severe bilateral ventriculomegaly measuring 27 mm.

A cesarean section was performed at 38 weeks of gestational age with a delivery of a female neonate with an appearance, pulse, grimace, activity, and respiration (APGAR) score of 9/10 at 1 and 5 minutes after birth, and no perinatal complications. Somatometry at birth was normal; with a weight of 2885g, length of 34.8 cm and head circumference of 47 cm. The metabolic screening was normal, and the child passed the neonatal auditory screening bilaterally.

The diagnosis of agenesis of the corpus callosum with no other associated cerebral malformations was confirmed in the neonatal period through transfontanellar cerebral US which revealed complete agenesis of the corpus callosum with symmetrical dilation of the occipital horns of the lateral ventricles (35/37mm).

At four months old, an MRI brain scan was performed which showed complete agenesis of the corpus callosum and the typical associated morphological changes. Thus, the third ventricle was in direct communication with the interhemispheric fissure, with a parallel orientation of the lateral ventricles, colpocephaly and dilation of the inferior-medial part of the temporal horns. The lateral ventricles with a “crescendo” configuration, the cingulate gyrus not defined, and the sulci on the medial surface of the cerebral hemispheres with a radiated orientation. No other brain malformations were apparent, namely evident malformations of cortical development or posterior fossa malformations.

Further genetic screening and metabolic screening were performed, but the child did not present any unusual craniofacial, digital, or neurocognitive features suggestive of a congenital syndrome or any other non-cerebral structural abnormality. Also, no evidence of visual or hearing impairment was observed. At 3 years old analysis by fluorescence in situ hybridization (FISH) was carried out to search for deletion on chromosome 4, in the critical region, where the genes involved in Wolf-Hirschhorn Syndrome (4p16.3) are located, which revealed a normal hybridization in both chromosomes, in the 20 cells analyzed. This result is compatible with the absence of a deletion in that region, for this level of resolution. Plus, cellular culture, standard cytogenetic analysis of GTG-banded chromosomes and

microscopic analysis revealed no chromosomal anomalies in the metaphases examined and normal karyotype of a female fetus. Additionally, ion exchange liquid chromatography without significant changes.

At four months old she was admitted to Centro Hospitalar Tâmega e Sousa for gastroesophageal reflux. The abdominal US showed slight gastric distension, but US criteria of hypertrophic pyloric stenosis were not observed, namely, the muscular layer did not exceed 2 mm. The remaining organs of the upper part of the abdomen showed no changes and an absence of free intraperitoneal fluid. Also, in the first year, she had a urinary tract infection with an US study with no changes.

The girl was followed in ophthalmology, in CHUPorto, she presented with hypopigmented ocular fundus, with no other alterations. The infant did cardiac and pelvic US checkups which were normal. She maintained regular neurodevelopment appointments in the Pediatric Department.

Development and Growth History

Regarding the infant's growth history, somatometry at 6 months, weight was in the 25-50th percentile, length in the 50-75th centile, and head circumference in the 75th percentile. At 9 months, her weight was in the 50-75th percentile, length in the 75th percentile and head circumference in the percentile 90. At 12 months, weight in the 50th percentile, length in the 50th percentile, and head circumference in the 90th percentile. At 15 months, weight in the 50th percentile, length in the 50th percentile, and head circumference in the 95th percentile. At two and a half years, weight at the 90th percentile, height at the 90th percentile and head circumference at the 95th percentile. At 19 months her weight and height were in the 90th percentile and head circumference in the 75-90th percentile. In conclusion, she had normal and adequate growth.

At 6, 9, 12, 15 and 19 months check-ups, she presented with normal motor development, vision-handling, hearing-language and social development. The psychomotor developmental milestones were adequate. Social smile at 2 months, head control at 3 months, unsupported sitting at 6-7 months. Food diversification occurred without intercurrences. Autonomous walking occurred at 12 months, first words at 12 months and started saying sentences before 24 months. There was no regression. She had control of daytime urinary sphincters and nighttime urinary sphincters at 2 years old.

She stayed with her mother until she was 18 months old and then with her maternal grandmother until she was three years old. By this age, she enrolled in kindergarten. When she was 5 years old, she

started elementary school. The difficulties pointed out by the teachers were of memorizing contents and slowness in carrying out tasks. She had afterschool support twice a week.

On neurodevelopment appointments, she demonstrated good contact, however, at an early stage demonstrated some inhibition in interacting and in carrying out certain tasks. However, as the consultation progressed, she felt more comfortable and started to interact more easily with the adult stranger.

Neurodevelopmental Evaluation

At 46 months old a formal neurodevelopmental assessment was performed using the Ruth Griffiths Developmental Scale. A score below 88 is below average, a score between 88 and 113 is average and a score higher than 114 is higher than average. Her performance was relatively homogeneous having a global development quotient QGD of 93, a result that places her within the average for her age group. The girl scored lower on the eye and hand coordination scale with a score of 89 and on the practical reasoning scale with a score of 88. Her locomotor scale score was 92, her personal-social scale score and her language scale score was 94 which place her within the average for her age group. The highest score was performance scale (manipulation, velocity and preciseness) with a score of 113.

At the age of 5, the neurodevelopmental assessment was performed again using the Ruth Griffiths Developmental Scale. A score below 88 is below average, a score between 88 and 113 is average and a score higher than 114 is higher than average. Her performance was relatively homogeneous having a global development quotient QGD of 97, a result that places her within the average for her age group. The patient scored below average on the practical reasoning scale with a score of 82. The locomotor scale score was 89, the personal-social scale score was 100, the language scale score was 104, the eye and hand coordination scale score was 100 and the performance scale (manipulation, velocity and preciseness) score was 104, which were normal and placed her within the average for her age group. Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R) was also performed, and she had an IQ of 94 which places her within the average for her age group, with a verbal score of 82 (low average) and reasoning of 109 (average).

At the age of 5, she was discharged from the neurodevelopmental consultation.

At the age of 10, the infant is referred again to a neurodevelopment appointment in CHUPorto with a letter from the school psychologist with the following information: “Student diagnosed with agenesis of the corpus callosum has learning difficulties with difficulty in interpretation and realization of tasks.”

Overall, her pattern of postnatal growth and neurocognitive development was normal. Furthermore, she did not show any neurological signs, behavioural or psychiatric disorders, or intellectual disability during her early childhood and school age. However, her school performance was below average, and she needed help after school.

Her mother refers that she shows little interest in activities and has slow execution of tasks at school. She sleeps in her room and sleeps about 6-7 hours per day. The mother refers that the girl has initial insomnia, she goes to bed at 9:30 pm and only falls asleep at 11:00 pm. The mother portrays the girl as always being in her world, likes to play alone, interacts barely, and bursts very easily. At home, at school or in public places she has no complaints due to anomalous behaviour. She is autonomous and helps with activities of daily living. She did no medication.

On physical examination, she showed no relevant alterations. The girl had adequate fine motor skills, adequate global motricity and proper verbal articulation. She reads fluently but doesn’t respect punctuation, can retell properly, and had proper calligraphy. Had very impulsive responses.

By this last visit of follow-up, DSM-5 criteria for attention-deficit/hyperactivity disorder (ADHD) were performed with an inattention score of 7/9 and a hyperactivity/impulsivity score of 5/9. Conners comprehensive behaviour rating scales and snap iv rating scale were performed and she scored for inattention.

Therefore, she was medicated with Melamil® Tripto and methylphenidate 30mg.

After four weeks, the mother reported that the child was calmer and less responsive and believed that she was more motivated at school. Additionally, there were fewer awakenings and noticed an improvement in her sleep with the medication.

Theoretical Revision

6. Corpus Callosum

The corpus callosum is the largest commissure of the brain and consists of white matter tracts that connect the frontal, parietal, temporal, occipital, insular, and limbic lobes and the basal ganglia [2] of the left and right cerebral hemispheres to each other. It comprises approximately 200 million heavily myelinated nerve fibers forming homotopic or heterotopic connections that allow the transfer of motor, sensory, and cognitive information between the two hemispheres.[3] Anatomically from anterior to posterior, it's divided into four parts, the rostrum, the genu, the body or trunk and the splenium, each responsible for connecting different areas of the cortex.[3] There may be a focal narrowing between the body and splenium within the posterior body, called the isthmus, a normal anatomic variation. [3]

Additionally, the rostrum and the genu fibers cross over and connect regions of the frontal lobe, the genu fibers cross via the forceps minor. [3] The splenium fibers connect the posterior parietal lobe and the occipital lobe, via the forceps major. The body fibers form the corona radiata.[3] Also, the corpus callosum forms a physical barrier to separate the two lateral ventricles in conjunction with the fornix.[3]

The primary function of the corpus callosum is to integrate and transfer information from both cerebral hemispheres;[3] these connections participate in an array of cognitive functions and the integration of complex motor and sensory information.[3]

The use of diffusion tensor imaging and tractography allowed the understanding of the diversity of interhemispheric callosal connections within each segment [4] as there seems to be a topographical organisation. Evidence suggests that the anterior callosal fibers transfer motor information between the frontal lobes, and the posterior fibers are involved in the processing of somatosensory information, hence, auditory via the isthmus and visual via the splenium.[3]

Lastly, the development of the corpus callosum occurs between 8 and 20 weeks of gestation. [5] Structural changes, such as an increase in the number of axons, axon diameter, and myelin continue throughout post-natal development and are most marked during childhood and adolescence.[3] Thus, some ipsilateral association fibers connecting the frontal with the temporal and parietal lobes do not achieve full myelination [6] until the third decade of life, though, at a much slower rate.[3]

7. Corpus callosum defects

Several abnormalities may affect the corpus callosum, including complete or partial agenesis, dysgenesis, hypoplasia or hyperplasia.[7] AgCC can occur isolated with no other associated abnormalities or in a complex presentation coexisting with other abnormalities. [7] [8]

It is one of the most frequent congenital brain malformations. Accordingly, evidence indicates it occurs in at least 1 in 4000 births.[9] However, it is likely underestimated as isolated AgCC exhibits subtle or no clinical symptoms and accidentally receives no medical attention. [10]

This brain malformation occurs due to disruption of neural development during the 7th to 20th embryonic weeks. [11]

Identifiable genetic causes are found in up to 45% of patients with AgCC,[11] including chromosomal anomalies in about 10-18% [12] and recognisable genetic syndromes in up to 35% of patients.[10] The genetics of this pathology is quite variable and reflects the underlying complexity of callosal development.

Furthermore, AgCC can be secondary to fetus insults like infections, vascular events or toxic substances. [10] [12] [8] For example, regarding fetal alcohol exposure, evidence indicates that alcohol exposure in utero decreases gliogenesis and glial-neuronal interactions processes critical to CC development. [9] Another examples of toxic factors are sodium valproate, cocaine and maternal phenylketonuria.

Furthermore, intracranial lipomas are rare callosal or pericallosal lesions, which arise from abnormal persistence of male differentiation of the primitive meninx, the embryonic precursor of the meninges. [13] Nearly 30–40% of intracranial lipomas occur in the pericallosal region. [14] [15]

8. Neuroimaging

The diagnosis of AgCC can be made during the pre and postnatal period. In most cases, the diagnosis is made during the prenatal period based on imaging tests.

Corpus callosum can be sought on US scans after about 16 to 17 weeks. Thus, screening for callosal abnormalities can be done on fetal morphological US, performed between the 18th and 22nd weeks of gestation. The absence of AgCC makes the diagnosis; however, it can be challenging to identify the absence or presence of the CC in practice. Therefore, although the CC can be assessed on US by direct

visualisation, reliance on screening for callosal abnormalities on routine scans is placed on indirect findings that results from brain arquitecture rearrangements. [12]

One of the main findings that raise suspicion about agenesis of the CC is the shape and size of the lateral ventricles. The absence of callosal axons, therefore, reduced white matter formation causes the occipital horns of the lateral ventricles to dilate.[14] In contrast, dilation of the frontal horns is limited by the firm caudate nuclei at their lateral borders.[14] Consequently, ventricles will have a teardrop shape reflecting the disproportionally enlarged occipital horns relative to the frontal horns, called colpocephaly. The third ventricle is often dilated and elevated, reaching the level of the lateral ventricles; its roof extends superiorly between the lateral ventricles and into the interhemispheric fissure and may be associated with a dorsal midline cyst.[14]

It's important to refer that ventriculomegaly becomes more common and increased in size with advancing gestational age. [14] [16]

Another finding is the lateral displacement of the bodies of the lateral ventricles due to the compression exerted by the presence bundle of Probst.[14] Probst bundles are aberrant bundles of axons that run in an anteroposterior direction rather than a left-right direction between the cerebral hemispheres. The inability of these axons to cross the midline results in anomalous axonal guidance and front-to-back projections within each hemisphere, rather than connecting between the hemispheres in the normal CC.

The concomitant absence of the CSP and the CC is due to their shared embryogenesis. Nonetheless, this is not specific to agenesis of the CC; it is also associated with holoprosencephaly, hydrocephalus, septal optic dysplasia, schizencephaly, encephalocele, porencephaly, and hydranencephaly. In individuals with partial agenesis of the CC, the CSP may appear normal, dysmorphic, or unusually short and wide in the axial plane.

The pericallosal artery can be visualised by the colour doppler just above the CC outlining its shape. In complete agenesis, the semicircular loop of the artery is lost, and the branches of the anterior cerebral artery ascend linearly. In partial agenesis, the pericallosal artery runs along the anterior part of the CC. Due to the absence of the posterior part of the CC, the course of this artery in this location undergoes an alteration introducing a new direction, posterior oblique and upward. However, diagnostic conclusions should not be based solely on an abnormal course of the pericallosal artery. [7]

Another indirect feature is the radial arrangement of the fissures in the inner region of the hemispheres. The absence of the CC results in the medial cerebral sulci being radially arranged perpendicular to the expected course of the CC, causing a sunburst sign on sagittal midline images. Also, the pericallosal sulcus and the cingulate sulcus are absent or present only as unconnected segments.

Lastly, AgCC can lead to increased separation of the cerebral hemispheres. This widening of the interhemispheric fissure can be seen on the US through three parallel echogenic lines.

Nonetheless, these anatomic findings can be seen to varying degrees in partial AgCC and tend to be more subtle. It's important to reference that not all of the above indirect signs must be present simultaneously for the diagnosis to be suspected.[7] [12]

Furthermore, the mid-sagittal and coronal scans of the fetal brain are the best planes to visualise the corpus callosum. Thus, when there is a suspicion of the diagnosis the next step in the evaluation is the fetal neurosonogram, in which the coronal and sagittal planes are obtained. [12] The fetal neurosonogram has a greater diagnostic potential than that of the standard transabdominal examination, however, this examination requires a grade of expertise. [17]

At last, after detecting agenesis of the corpus callosum, it is necessary to access if it is associated with other malformations or genetic anomalies or if it is the only alteration present. In this situation, a fetal MRI should be performed to search for associated anomalies, namely neuronal migration disorders and heterotopias. In a recent systematic review, prenatal MRI was associated with detecting additional abnormalities in 22.5% of cases compared with ultrasonography. [8] The most common anomalies missed in the US and diagnosed only at fetal MRI were cortical and posterior fossa anomalies.

The association of AgCC with other cerebral anomalies is associated with a worse prognosis. Therefore, this highlights the importance of MRI assessment, as such undetected abnormalities in the US can significantly impact the postnatal outcome of these children.

Moreover, some abnormalities are missed at fetal MRI and detected only after birth. So it's important to specify during parental counselling that in 13-15% of cases associated anomalies will be detected postnatally.[18] Thus, a study shows that symptoms and manifestations associated with agenesis and dysgenesis of the corpus callosum cannot be explained by the morphological changes only seen in conventional MRI.[19]

9. Associated Abnormalities

As referred above, the CC development begins from 8 weeks onwards; therefore, other CNS anomalies occur frequently. Additional CNS abnormalities are reported in 45% to 80% of fetuses, including Chiari II and Dandy-Walker malformation, holoprosencephaly, encephalocele, arachnoid cyst, heterotopias and neuronal migration disorders. [12] [21]

Likewise, extracranial abnormalities are seen in up to 60%, including facial abnormalities, congenital heart disease, and skeletal and genitourinary abnormalities. [12]

Also, in many chromosomal disorders, particularly trisomies 8, 11 and 13, AgCC is a common component.[6]

AgCC has been associated with several syndromes with autosomal dominant, autosomal recessive, or X-linked mode of inheritance. [8] Though, given the uncertain prevalence of AgCC, it is tough to establish the frequency of underlying genetic syndromes.[8] The more common genetic causes of callosal agenesis are Aicardi and Andermann. Aicardi syndrome is found almost exclusively in girls as it is inherited as an X-linked dominant trait; it is characterised by the presence of AgCC associated with chorioretinal abnormalities, infantile seizures, and mental retardation. Andermann syndrome is a rare autosomal recessive disorder characterised by AgCC, progressive motor-sensory neuropathy, and mental retardation.[8]

10. Prenatal screening, Counselling and Prognosis

Investigation of suspected cases includes detailed CNS and somatic US, MRI, karyotype, chromosomal microarray analysis (CMA), and screening for TORCH infections. Thus, AgCC has been reported associated with cytomegalovirus, toxoplasmosis, rubella, and influenza virus.

Furthermore, AgCC has been associated with several chromosomal rearrangements, for example, chromosomal deletions. Nevertheless, studies are not consistent in reporting chromosomal analysis, so it is difficult to specify the incidence of chromosomal abnormalities. Evidence suggests that this high risk of chromosomal abnormalities is confined to complex cases.

Therefore, it's recommended to consider amniocentesis for chromosomal analysis using CMA[8], genetic testing, as well as screening for congenital infections, especially in those with multiple defects detected by imaging.[22]

Studies suggest that BDNF, SLC1A2, and PAX6 may be involved in the development of isolated AgCC.[23] Thus, CMA is a feasible technology for prenatal diagnosis of isolated AgCC.[23]

The prognosis is influenced by multiple factors such as type of agenesis, damaged part of the CC, associated defects, and the residual interhemispheric transfer through other commissures (anterior, posterior, or hippocampal).[24]

In the context of genetic abnormalities or polimalformative syndromes, the prognosis is poor and related to the pathology in question.

Prognosis in apparently isolated AgCC can be good in 65% to 75% of cases. However, it is difficult to be sure of the prognosis due to the variation in neurodevelopmental outcomes that neuroanatomic findings cannot predict. Nevertheless, in some cases, subtle neuropsychologic, perceptual, and motor deficits do not become apparent until later in life.[25] Therefore, long-term follow-up, especially regarding social interactions and school performance is important to provide better prognostic information to families.[25] There is no agreement in the literature regarding the timing and frequency of follow-up in fetuses with AgCC.

Consequently, after the diagnosis of pathology of the CC, parental counselling is extremely difficult due to the vast clinical presentation, ranging from cases of patients with normal neurodevelopment and patients with severe neurological disabilities.

11. Post-natal development of this pathology

The cognitive, behavioural, and neurological consequences of AgCC are wide-ranging. Studies have tried to group neuroanatomical findings and subsequently relate these to the behavioural symptoms, however, the neurodevelopment of individuals with AgCC is extremely variable, even among patients with similar neuroanatomical profiles.[9] For this reason, it is highly challenging to assess the neurological development of individuals with this pathology.

The isolated presentation of AgCC is associated with better neurological outcomes and, consequently, better prognosis.

A wide range of clinical presentations are associated with cases of isolated AgCC, covering cases of individuals with completely normal neurodevelopment to cases with severe neurological impairment. Thus, patients can have normal intelligence quotient but may have some cognitive deficits. The most

prevalent clinical implications reported in symptomatic patients are epilepsy, motor impairment and intellectual disability, however, an asymptomatic course of the disease is even more common. [1]

In individuals with AgCC, the functions involved are hemispherically lateralized (emotions, language, visuospatial processing). If the development of the corpus callosum is impaired, the normal interaction and competition between the hemispheres are abolished, resulting in alternative routes in the adult brain. [26]

Thus, a systematic review by Brown WS et al systematized the main domains affected in patients with isolated AgCC which, in turn, contribute to more specific neuropsychological and psychosocial deficits. Thus, the study suggests that isolated AgCC is associated with a core syndrome involving the reduced interhemispheric transfer of sensory-motor information, increased cognitive processing time, and deficient processing of complex information and unfamiliar tasks, resulting in amplified vulnerability to increases in cognitive demands. [11] These three domains of dysfunction are not independent. Thus, reduced interhemispheric interactions likely contribute to slower processing time and difficulty in complex problem solving, which are interrelated. These core deficits can lead to several cognitive deficits and changes in patients' behaviour. [11]

Thus, neuropsychological impairments include difficulties in encoding verbal and visual memory information [23], in the spontaneous retrieval of newly learned information, the adequate understanding of non-literal and complex language, difficulty comprehending non-literal language and humour [28] [29], deficits in learning and memory [30], in formulating strategies and in the effective application of imagination and creativity.

The CC is involved in the neural organization of language. [31] Thus, in basic language functioning, various subtle deficits have been described, including difficulties in understanding idioms, proverbs, pragmatic language, spontaneous interpretation of proverbs [32] and narrative humour as they tend to ignore the second sense of narratives or conversations.[32] Likewise, verbal memory functions, including encoding, retention and retrieval are reduced in many individuals with AgCC.

Social functioning involves multiple complex cognitive processes and requires a high degree of interhemispheric processing. Thus, individuals with AgCC are reported to exhibit emotional immaturity, they tend to misconstrue social information, and misunderstand the mental states of others within complex social contexts, including problems with and in recognizing emotions in faces, theory of mind, and inhibitory control. [26] [33] [34] [35] [36] [37] The impairments in social skills and problems of

personal insight, that these patients may present are referred by the parents as the resources that most interfere in their children's daily lives.[38]

However, individuals with isolated AgCC do not have linguistic impairments related to naming, receptive, lexical language and reading skills. Passar este parágrafo para o fim da página 14 após a frase: Likewise, verbal memory functions, including encoding, retention and retrieval are reduced in many individuals with AgCC

Furthermore, patients exhibit deficits in high-level cognitive functions, including slower reaction times and processing speed [39], difficulties in abstract reasoning, problem-solving and generalization.

AgCC has been linked to various neuropsychiatric disorders including ADHD, schizophrenia, obsessive-compulsive disorder and bipolar disorder.[40]

Many of the social and behavioural problems associated with AgCC are also associated with autism spectrum disorder. [34] Research suggests that high-functioning children with autism and children with isolated AgCC have certain forms of social disability in common. [34] However, it is important to note that the causal relationship between callosal agenesis and autism remains unclear. [41]

Additionally, evidence demonstrates the involvement of the CC in attentional skills. Although the etiology of ADHD remains unclear, one of the most replicated structural alterations in attention-deficit/hyperactivity disorder is reduced callosal size and slowed interhemispheric transfer. [42] [43] [44]

Children with isolated AgCC may present with different degrees of impairment becoming more evident only in their second decade of life. [45] Since the corpus callosum undergoes significant myelinization and functional development into the teenage years, the neuropsychological and psychosocial outcomes of AgCC seem to be more evident with age as individuals with CC increase reliance on callosal connectivity. The core deficits of AgCC described above may not become pronounced relative to peers before late childhood. Therefore, even in patients with no apparent deficits, subtle neuropsychological alterations may occur as the cognitive demand increases with age.

12. Conclusion

Malformations of the nervous system are unique, no two individual cases are identical, even when categorized as the same anatomical malformation.[6] In AgCC the heterogeneity of presentations can be explained by the difficulty in confirming the isolated nature of AgCC prenatally, the small size of retrospective studies and the lack of standardization in the follow-up of affected infants. [47] Postnatal

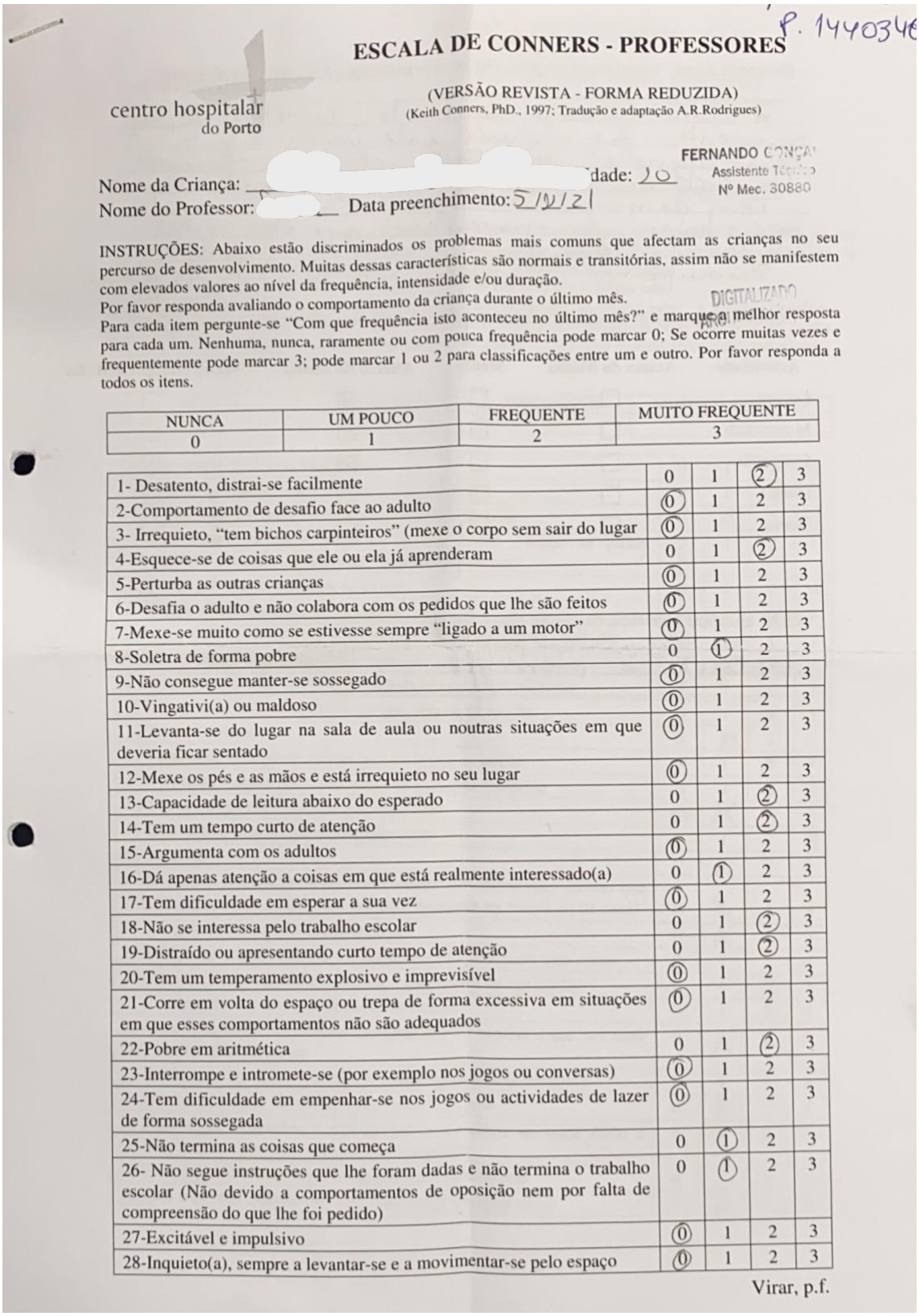
MRI and genetic analysis can add complementary information to prenatal data to support the outcome and help orient clinical management.[45]

Furthermore, as seen above the expression of deficits can vary throughout life. This can lead to late identification of neurocognitive alterations and to a delayed establishment of rehabilitative strategies aimed to enhance compensatory functions in affected individuals. These variations occur not only because of neuroanatomical changes but also depending on the characteristics and context of each individual.

Therefore, patients with this condition require close neurocognitive follow-up despite having normal cognitive function during childhood. Monitoring with language and speech assessment is important to identify those who will require support such as special medical needs or educational support. Consequently, a longitudinal neurocognitive follow-up is recommended in all individuals diagnosed with AgCC.[48] Duration of follow-up must be long enough to diagnose such difficulties and offer appropriate help.

Finally, complete and clear information should be provided to parents mentioning the difficulties of affirming prenatally that AgCC is isolated and the possibility of deficits, even if IQ remains within the normal range.[46] To achieve more accurate prognosis assessments in prenatal practice, many research fields will need to be explored to fully define this syndrome. [49]

Figure 1 - Conners' Teacher Rating Scale



P. 1440346

ESCALA DE CONNERS - PROFESSORES

centro hospitalar do Porto

(VERSÃO REVISTA - FORMA REDUZIDA)
(Keith Conners, PhD., 1997; Tradução e adaptação A.R.Rodrigues)

FERNANDO CONÇA
Assistente Técnico
Nº Mec. 30880

Nome da Criança: [redacted] dade: 20
Nome do Professor: [redacted] Data preenchimento: 5/11/21

INSTRUÇÕES: Abaixo estão discriminados os problemas mais comuns que afectam as crianças no seu percurso de desenvolvimento. Muitas dessas características são normais e transitórias, assim não se manifestem com elevados valores ao nível da frequência, intensidade e/ou duração.
Por favor responda avaliando o comportamento da criança durante o último mês.
Para cada item pergunte-se "Com que frequência isto aconteceu no último mês?" e marque a melhor resposta para cada um. Nenhuma, nunca, raramente ou com pouca frequência pode marcar 0; Se ocorre muitas vezes e frequentemente pode marcar 3; pode marcar 1 ou 2 para classificações entre um e outro. Por favor responda a todos os itens.

DIGITALIZADO

NUNCA	UM POUCO	FREQUENTE	MUITO FREQUENTE
0	1	2	3

1- Desatento, distrai-se facilmente	0	1	(2)	3
2-Comportamento de desafio face ao adulto	(0)	1	2	3
3- Irrequieto, "tem bichos carpinteiros" (mexe o corpo sem sair do lugar	(0)	1	2	3
4-Esquece-se de coisas que ele ou ela já aprenderam	0	1	(2)	3
5-Perturba as outras crianças	(0)	1	2	3
6-Desafia o adulto e não colabora com os pedidos que lhe são feitos	(0)	1	2	3
7-Mexe-se muito como se estivesse sempre "ligado a um motor"	(0)	1	2	3
8-Soletra de forma pobre	0	(1)	2	3
9-Não consegue manter-se sossegado	(0)	1	2	3
10-Vingativi(a) ou maldoso	(0)	1	2	3
11-Levanta-se do lugar na sala de aula ou noutras situações em que deveria ficar sentado	(0)	1	2	3
12-Mexe os pés e as mãos e está irrequieto no seu lugar	(0)	1	2	3
13-Capacidade de leitura abaixo do esperado	0	1	(2)	3
14-Tem um tempo curto de atenção	0	1	(2)	3
15-Argumenta com os adultos	(0)	1	2	3
16-Dá apenas atenção a coisas em que está realmente interessado(a)	0	(1)	2	3
17-Tem dificuldade em esperar a sua vez	(0)	1	2	3
18-Não se interessa pelo trabalho escolar	0	1	(2)	3
19-Distraído ou apresentando curto tempo de atenção	0	1	(2)	3
20-Tem um temperamento explosivo e imprevisível	(0)	1	2	3
21-Corre em volta do espaço ou trepa de forma excessiva em situações em que esses comportamentos não são adequados	(0)	1	2	3
22-Pobre em aritmética	0	1	(2)	3
23-Interrompe e intromete-se (por exemplo nos jogos ou conversas)	(0)	1	2	3
24-Tem dificuldade em empenhar-se nos jogos ou actividades de lazer de forma sossegada	(0)	1	2	3
25-Não termina as coisas que começa	0	(1)	2	3
26- Não segue instruções que lhe foram dadas e não termina o trabalho escolar (Não devido a comportamentos de oposição nem por falta de compreensão do que lhe foi pedido)	0	(1)	2	3
27-Excitável e impulsivo	(0)	1	2	3
28-Inquieto(a), sempre a levantar-se e a movimentar-se pelo espaço	(0)	1	2	3

Virar, p.f.

- Descreva agora, sucintamente, quais são as suas preocupações com o(a) aluno(a):

A aluna [redacted] é muito introvertida, raramente faz alguma intervenção, não participando em quase alguma. Mesmo lhe solicitada a fazê-lo, dificilmente intervem. Tem demonstrado bom comportamento. No contínuo do ano anterior, que pela alpha mentia com frequência, não o tem feito. Preocupa-me a apatia com que está nas aulas.

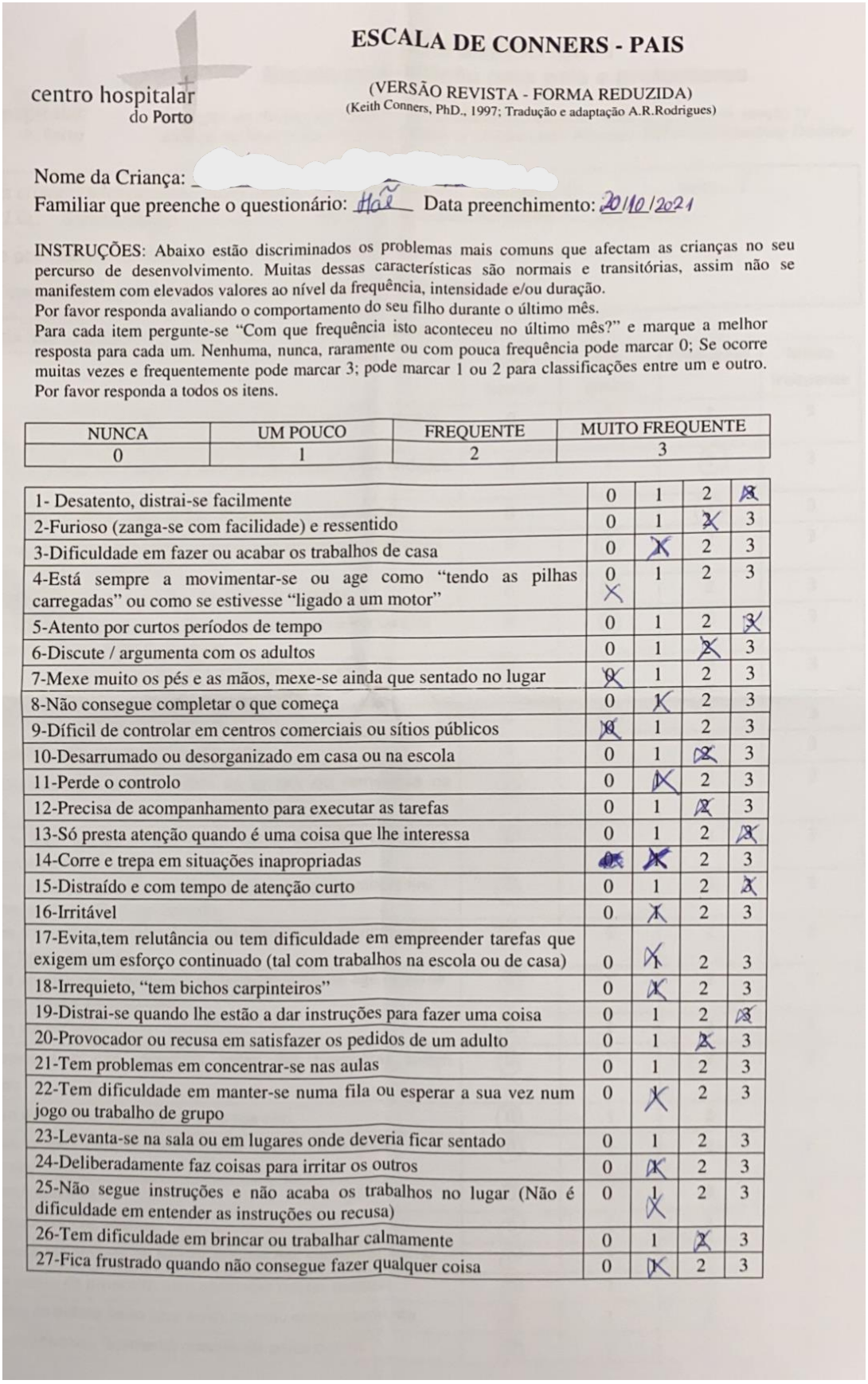
- Como situa as competências académicas deste(a) com o(a) aluno(a):

Actividade	Acima da Média	Média	Abaixo da Média	Muito abaixo da Média
Leitura	☐	☐	☒	☐
Matemática	☐	☐	☒	☐
Caligrafia	☐	☐	☒	☐
Ditado	☐	☐	☐	☐
Outras	☐	☐	☐	☐

- O(A) aluno(a) beneficia de algum tipo de apoio educativo? Qual(is)?

A aluna beneficia de apoios a Português e Matemática

Figure 2 - Conners' Parent Rating Scale



centro hospitalar do Porto

ESCALA DE CONNERS - PAIS

(VERSÃO REVISTA - FORMA REDUZIDA)
(Keith Conners, PhD., 1997; Tradução e adaptação A.R.Rodrigues)

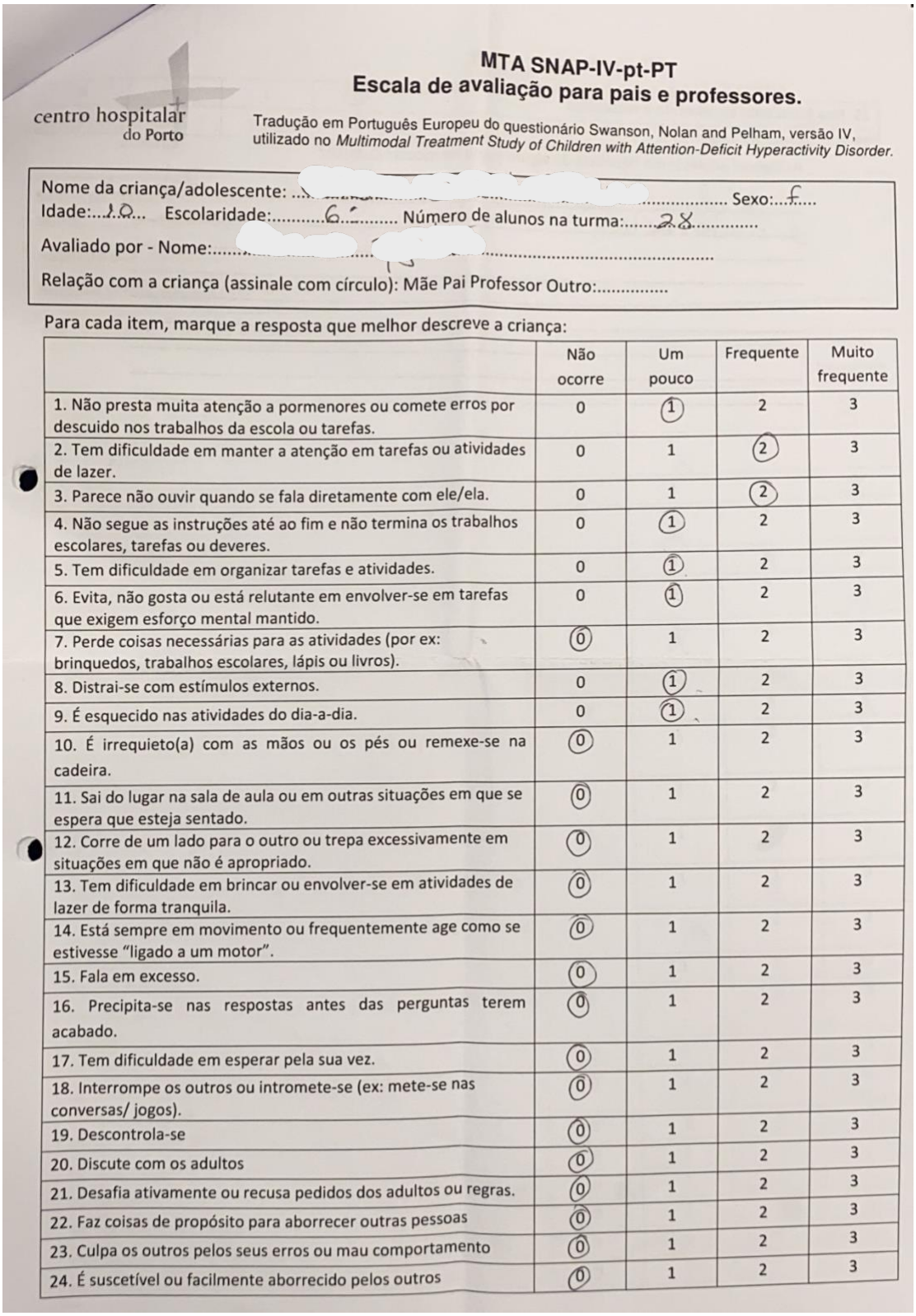
Nome da Criança: [redacted]
Familiar que preenche o questionário: Mãe Data preenchimento: 20/10/2021

INSTRUÇÕES: Abaixo estão discriminados os problemas mais comuns que afectam as crianças no seu percurso de desenvolvimento. Muitas dessas características são normais e transitórias, assim não se manifestem com elevados valores ao nível da frequência, intensidade e/ou duração.
Por favor responda avaliando o comportamento do seu filho durante o último mês.
Para cada item pergunte-se "Com que frequência isto aconteceu no último mês?" e marque a melhor resposta para cada um. Nenhuma, nunca, raramente ou com pouca frequência pode marcar 0; Se ocorre muitas vezes e frequentemente pode marcar 3; pode marcar 1 ou 2 para classificações entre um e outro.
Por favor responda a todos os itens.

NUNCA	UM POUCO	FREQUENTE	MUITO FREQUENTE
0	1	2	3

1- Desatento, distrai-se facilmente	0	1	2	3
2-Furioso (zanga-se com facilidade) e ressentido	0	1	2	3
3-Dificuldade em fazer ou acabar os trabalhos de casa	0	1	2	3
4-Está sempre a movimentar-se ou age como "tendo as pilhas carregadas" ou como se estivesse "ligado a um motor"	0	1	2	3
5-Atento por curtos períodos de tempo	0	1	2	3
6-Discute / argumenta com os adultos	0	1	2	3
7-Mexe muito os pés e as mãos, mexe-se ainda que sentado no lugar	0	1	2	3
8-Não consegue completar o que começa	0	1	2	3
9-Díficil de controlar em centros comerciais ou sítios públicos	0	1	2	3
10-Desarrumado ou desorganizado em casa ou na escola	0	1	2	3
11-Perde o controlo	0	1	2	3
12-Precisa de acompanhamento para executar as tarefas	0	1	2	3
13-Só presta atenção quando é uma coisa que lhe interessa	0	1	2	3
14-Corre e trepa em situações inapropriadas	0	1	2	3
15-Distraído e com tempo de atenção curto	0	1	2	3
16-Irritável	0	1	2	3
17-Evita,tem relutância ou tem dificuldade em empreender tarefas que exigem um esforço continuado (tal com trabalhos na escola ou de casa)	0	1	2	3
18-Irrequieto, "tem bichos carpinteiros"	0	1	2	3
19-Distrai-se quando lhe estão a dar instruções para fazer uma coisa	0	1	2	3
20-Provocador ou recusa em satisfazer os pedidos de um adulto	0	1	2	3
21-Tem problemas em concentrar-se nas aulas	0	1	2	3
22-Tem dificuldade em manter-se numa fila ou esperar a sua vez num jogo ou trabalho de grupo	0	1	2	3
23-Levanta-se na sala ou em lugares onde deveria ficar sentado	0	1	2	3
24-Deliberadamente faz coisas para irritar os outros	0	1	2	3
25-Não segue instruções e não acaba os trabalhos no lugar (Não é dificuldade em entender as instruções ou recusa)	0	1	2	3
26-Tem dificuldade em brincar ou trabalhar calmamente	0	1	2	3
27-Fica frustrado quando não consegue fazer qualquer coisa	0	1	2	3

Figure 3 - Swanson, Nolan and Pelham Teacher and Parent (SNAP) Rating Scale-IV Rating Scale - Teacher



centro hospitalar do Porto

MTA SNAP-IV-pt-PT
Escala de avaliação para pais e professores.

Tradução em Português Europeu do questionário Swanson, Nolan and Pelham, versão IV, utilizado no *Multimodal Treatment Study of Children with Attention-Deficit Hyperactivity Disorder.*

Nome da criança/adolescente: [redacted] Sexo: f
Idade: 10 Escolaridade: 6.º Número de alunos na turma: 28
Avaliado por - Nome: [redacted]
Relação com a criança (assinale com círculo): Mãe Pai Professor Outro:.....

Para cada item, marque a resposta que melhor descreve a criança:

	Não ocorre	Um pouco	Frequente	Muito frequente
1. Não presta muita atenção a pormenores ou comete erros por descuido nos trabalhos da escola ou tarefas.	0	(1)	2	3
2. Tem dificuldade em manter a atenção em tarefas ou atividades de lazer.	0	1	(2)	3
3. Parece não ouvir quando se fala diretamente com ele/ela.	0	1	(2)	3
4. Não segue as instruções até ao fim e não termina os trabalhos escolares, tarefas ou deveres.	0	(1)	2	3
5. Tem dificuldade em organizar tarefas e atividades.	0	(1)	2	3
6. Evita, não gosta ou está relutante em envolver-se em tarefas que exigem esforço mental mantido.	0	(1)	2	3
7. Perde coisas necessárias para as atividades (por ex: brinquedos, trabalhos escolares, lápis ou livros).	(0)	1	2	3
8. Distrai-se com estímulos externos.	0	(1)	2	3
9. É esquecido nas atividades do dia-a-dia.	0	(1)	2	3
10. É irrequieto(a) com as mãos ou os pés ou remexe-se na cadeira.	(0)	1	2	3
11. Sai do lugar na sala de aula ou em outras situações em que se espera que esteja sentado.	(0)	1	2	3
12. Corre de um lado para o outro ou trepa excessivamente em situações em que não é apropriado.	(0)	1	2	3
13. Tem dificuldade em brincar ou envolver-se em atividades de lazer de forma tranquila.	(0)	1	2	3
14. Está sempre em movimento ou frequentemente age como se estivesse "ligado a um motor".	(0)	1	2	3
15. Fala em excesso.	(0)	1	2	3
16. Precipita-se nas respostas antes das perguntas terem acabado.	(0)	1	2	3
17. Tem dificuldade em esperar pela sua vez.	(0)	1	2	3
18. Interrompe os outros ou intromete-se (ex: mete-se nas conversas/ jogos).	(0)	1	2	3
19. Descontrola-se	(0)	1	2	3
20. Discute com os adultos	(0)	1	2	3
21. Desafia ativamente ou recusa pedidos dos adultos ou regras.	(0)	1	2	3
22. Faz coisas de propósito para aborrecer outras pessoas	(0)	1	2	3
23. Culpa os outros pelos seus erros ou mau comportamento	(0)	1	2	3
24. É suscetível ou facilmente aborrecido pelos outros	(0)	1	2	3

25. Fica facilmente enraivecido e ressentido	(0)	1	2	3
26. É rancoroso ou vingativo	(0)	1	2	3

A criança/ adolescente beneficia de algum apoio na escola? Qual(is)?

A aluna beneficia de oficinas a Português e matemática.

13. Bibliography

1. Hofman J, Hutny M, Sztuba K, Paprocka J. Corpus Callosum Agenesis: An Insight into the Etiology and Spectrum of Symptoms. *Brain Sci*. 2020;10(9):625. doi:10.3390/brainsci10090625

2. Shah A, Jhawar S, Goel A, Goel A. Corpus Callosum and Its Connections: A Fiber Dissection Study. *World Neurosurg*. 2021;151:e1024-e1035. doi:10.1016/j.wneu.2021.05.047

3. Goldstein A, Covington BP, Mahabadi N, Mesfin FB. Neuroanatomy, Corpus Callosum. In: *StatPearls*. StatPearls Publishing; 2022. Accessed February 5, 2022. http://www.ncbi.nlm.nih.gov/books/NBK448209/

4. Edwards TJ, Sherr EH, Barkovich AJ, Richards LJ. Clinical, genetic and imaging findings identify new causes for corpus callosum development syndromes. *Brain*. 2014;137(6):1579-1613. doi:10.1093/brain/awt358

5. Sadler TW, Langman J. *Langman's Medical Embryology.* Lippincott William & Wilkins; 2010.

6. B. Sarnat H, Flores-Sarnat L. Developmental Disorders of the Nervous System. In: *Bradley's Neurology in Clinical Practice*. Elsevier; 2016.

7. Rotmensch S, Monteagudo A. Agenesis of the Corpus Callosum. *Am J Obstet Gynecol*. 2020;223(6):B17-B22. doi:10.1016/j.ajog.2020.08.179

8. Santo S, D'Antonio F, Homfray T, et al. Counseling in fetal medicine: agenesis of the corpus callosum: Agenesis of the corpus callosum. *Ultrasound Obstet Gynecol*. 2012;40(5):513-521. doi:10.1002/uog.12315

9. Paul LK, Brown WS, Adolphs R, et al. Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. *Nat Rev Neurosci*. 2007;8(4):287-299. doi:10.1038/nrn2107

10. Unterberger I, Bauer R, Walser G, Bauer G. Corpus callosum and epilepsies. *Seizure*. 2016;37:55-60. doi:10.1016/j.seizure.2016.02.012

11. Brown WS, Paul LK. The Neuropsychological Syndrome of Agenesis of the Corpus Callosum. *J Int Neuropsychol Soc*. 2019;25(3):324-330. doi:10.1017/S135561771800111X

12. Toi A, Levine D. The Fetal Brain. In: *Diagnostic Ultrasound*. 5th ed. ; :1166-1215.

13. Mahajan PS, Al Moosawi NM, Hasan IA. A Rare Case of Pericallosal Lipoma Associated with Bilaterally Symmetrical Lateral Ventricular Choroid Plexus Lipomas without Corpus Callosal Anomalies. *J Clin Imaging Sci*. 2013;3:69. doi:10.4103/2156-7514.124109

14. Park SE, Choi DS, Shin HS, et al. Splenial Lesions of the Corpus Callosum: Disease Spectrum and MRI Findings. *Korean J Radiol*. 2017;18(4):710. doi:10.3348/kjr.2017.18.4.710

15. Ho ML, Moonis G, Ginat DT, Eisenberg RL. Lesions of the Corpus Callosum. *Am J Roentgenol*. 2013;200(1):W1-W16. doi:10.2214/AJR.11.8080

16. Paladini D, Pastore G, Cavallaro A, Massaro M, Nappi C. Agenesis of the fetal corpus callosum: sonographic signs change with advancing gestational age: Changes in sonographic signs of fetal ACC. *Ultrasound Obstet Gynecol*. 2013;42(6):687-690. doi:10.1002/uog.12506

17. Sonographic examination of the fetal central nervous system: guidelines for performing the 'basic examination' and the 'fetal neurosonogram.' *Ultrasound Obstet Gynecol*. 2007;29(1):109-116. doi:10.1002/uog.3909

18. Sileo FG, Di Mascio D, Rizzo G, et al. Role of prenatal magnetic resonance imaging in fetuses with isolated agenesis of corpus callosum in the era of fetal neurosonography: A systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. 2021;100(1):7-16. doi:10.1111/aogs.13958

19. El Ameen N, Ibrahim M, Mounir S. Fiber tractography and diffusion tensor imaging in children with agenesis and dysgenesis of corpus callosum: A clinico-radiologic correlation. *Int J Pediatr*. 2019;(Online First). doi:10.22038/ijp.2019.39349.3354

20. Toi A. Chapter 34 - The Fetal Brain. :3.

21. M. Rumack C, K. Auckland A. Neonatal and Infant Brain Imaging. In: *Diagnostic Ultrasound*.

22. Guadarrama-Ortiz P, Choreño-Parra JA, de la Rosa-Arredondo T. Isolated agenesis of the corpus callosum and normal general intelligence development during postnatal life: a case report and review of the literature. *J Med Case Reports*. 2020;14(1):28. doi:10.1186/s13256-020-2359-2

23. She Q, Fu F, Guo X, Tan W, Liao C. Genetic testing in fetuses with isolated agenesis of the corpus callosum. *J Matern Fetal Neonatal Med*. 2021;34(14):2227-2234. doi:10.1080/14767058.2019.1660769

24. Nica E, Mitran M, Marinescu B. Neurodevelopmental outcome in children with a prenatal diagnosis of agenesis of corpus callosum. 2021;(4):5.

25. VOLPE P, VOTINO C, FANELLI T, DE ROBERTIS V, REMBOUSKOS G, ROSSI A. Corpus Callosum and Septum Pellucidum Anomalies. In: *Obstetric Imaging Fetal Diagnosis and Care*. Elsevier; 2018. Accessed February 13, 2022. https://www.sciencedirect.com/science/book/9780323445481

26. Lábadi B, Beke AM. Mental State Understanding in Children with Agenesis of the Corpus Callosum. *Front Psychol*. 2017;8. doi:10.3389/fpsyg.2017.00094

27. Paul LK, Erickson RL, Hartman JA, Brown WS. Learning and memory in individuals with agenesis of the corpus callosum. *Neuropsychologia*. 2016;86:183-192. doi:10.1016/j.neuropsychologia.2016.04.013

28. Brown WS, Paul LK, Symington M, Dietrich R. Comprehension of humor in primary agenesis of the corpus callosum. *Neuropsychologia*. 2005;43(6):906-916. doi:10.1016/j.neuropsychologia.2004.09.008

29. Turk AA, Brown WS, Symington M, Paul LK. Social narratives in agenesis of the corpus callosum: Linguistic analysis of the Thematic Apperception Test. *Neuropsychologia*. 2010;48(1):43-50. doi:10.1016/j.neuropsychologia.2009.08.009

30. Erickson RL, Paul LK, Brown WS. Verbal learning and memory in agenesis of the corpus callosum. *Neuropsychologia*. 2014;60:121-130. doi:10.1016/j.neuropsychologia.2014.06.003

31. Bartha-Doering L, Schwartz E, Kollndorfer K, et al. Effect of corpus callosum agenesis on the language network in children and adolescents. *Brain Struct Funct*. 2021;226(3):701-713. doi:10.1007/s00429-020-02203-6

32. Rehmel JL, Brown WS, Paul LK. Proverb comprehension in individuals with agenesis of the corpus callosum. *Brain Lang*. 2016;160:21-29. doi:10.1016/j.bandl.2016.07.001

33. Brown WS, Burnett KA, Vaillancourt A, Paul LK. Appreciation of Social Norms in Agenesis of the Corpus Callosum. *Arch Clin Neuropsychol*. 2021;36(7):1367-1373. doi:10.1093/arclin/acab003

34. Badaruddin DH, Andrews GL, Bolte S, et al. Social and Behavioral Problems of Children with Agenesis of the Corpus Callosum. *Child Psychiatry Hum Dev*. Published online 2007:16.

35. Symington SH, Paul LK, Symington MF, Ono M, Brown WS. Social cognition in individuals with agenesis of the corpus callosum. *Soc Neurosci*. 2010;5(3):296-308. doi:10.1080/17470910903462419

36. Bridgman MW, Brown WS, Spezio ML, Leonard MK, Adolphs R, Paul LK. Facial emotion recognition in agenesis of the corpus callosum. *J Neurodev Disord*. 2014;6(1):32. doi:10.1186/1866-1955-6-32

37. Paul L. Social processing deficits in agenesis of the corpus callosum: narratives from the Thematic Apperception Test. *Arch Clin Neuropsychol*. 2004;19(2):215-225. doi:10.1016/S0887-6177(03)00024-6

38. Anderson LB, Paul LK, Brown WS. Emotional Intelligence in Agenesis of the Corpus Callosum. *Arch Clin Neuropsychol*. Published online January 23, 2017:acn;acx001v1. doi:10.1093/arclin/acx001

39. Marco EJ, Harrell KM, Brown WS, et al. Processing Speed Delays Contribute to Executive Function Deficits in Individuals with Agenesis of the Corpus Callosum. *J Int Neuropsychol Soc*. 2012;18(03):521-529. doi:10.1017/S1355617712000045

40. Mohapatra S, Panda UK, Sahoo AJ, Dey S, Rath N. Neuropsychiatric manifestations in a child with agenesis of the corpus callosum. *J Neurosci Rural Pract*. 2015;6(03):456-457. doi:10.4103/0976-3147.158758

41. Paul LK, Corsello C, Kennedy DP, Adolphs R. Agenesis of the corpus callosum and autism: a comprehensive comparison. *Brain*. 2014;137(6):1813-1829. doi:10.1093/brain/awu070

42. Brown WS, Panos A, Paul LK. Attention, impulsivity, and vigilance in agenesis of the corpus callosum. *Neuropsychology*. 2020;34(7):744-749. doi:10.1037/neu0000685

43. Semrud-Clikeman M, Filipek PA, Biederman J, et al. Attention-Deficit Hyperactivity Disorder: Magnetic Resonance Imaging Morphometric Analysis of the Corpus Callosum. *J Am Acad Child Adolesc Psychiatry*. 1994;33(6):875-881. doi:10.1097/00004583-199407000-00014

44. Luders E, Kurth F, Das D, et al. Associations between corpus callosum size and ADHD symptoms in older adults: The PATH through life study. *Psychiatry Res Neuroimaging*. 2016;256:8-14. doi:10.1016/j.pscychresns.2016.08.009

45. Romaniello R, Arrigoni F, De Salvo P, et al. Long-term follow-up in a cohort of children with isolated corpus callosum agenesis at fetal MRI. *Ann Clin Transl Neurol*. 2021;8(12):2280-2288. doi:10.1002/acn3.51484

46. Moutard ML, Kieffer V, Feingold J, et al. Agenesis of corpus callosum: prenatal diagnosis and prognosis. *Childs Nerv Syst*. 2003;19(7-8):471-476. doi:10.1007/s00381-003-0781-6

47. Mangione R, Godard P, Capron C, Mirlesse V, Lacombe D, Duyme M. Neurodevelopmental outcome following prenatal diagnosis of an isolated anomaly of the corpus callosum: Anomaly of corpus callosum and neurodevelopment. *Ultrasound Obstet Gynecol*. 2011;37(3):290-295. doi:10.1002/uog.8882

48. Folliot-Le Doussal L, Chadie A, Brasseur-Daudruy M, Verspyck E, Saugier-Veber P, Marret S. Neurodevelopmental outcome in prenatally diagnosed isolated agenesis of the corpus callosum. *Early Hum Dev*. 2018;116:9-16. doi:10.1016/j.earlhumdev.2017.10.004

49. Moutard ML, Kieffer V, Feingold J, et al. Isolated corpus callosum agenesis: a ten-year follow-up after prenatal diagnosis (How are the children without corpus callosum at 10 years of age?): Isolated corpus callosum agenesis: a ten-year follow-up after prenatal diagnosis. *Prenat Diagn*. 2012;32(3):277-283. doi:10.1002/pd.3824

Appendix - Approval given by the Ethics Committee of Centro Hospitalar Universitário do Porto

REPÚBLICA PORTUGUESA
SAÚDE

SNS SERVIÇO NACIONAL DE SAÚDE

centro hospitalar do Porto

Exma. Sra. Mafalda Calheiros
Estudante do ICBAS

ASSUNTO: Caso Clínico - MIM - **"Congenital disorders of the corpus callosum and development during postnatal life: a case report and review of the literature "** – N/ REF.ª 2021.335 (CC-DEFI/288-CE)

O Conselho de Administração do CHUPorto autoriza a realização do estudo acima mencionado, a realizar no Serviço de Obstetrícia desta Instituição e tendo como Investigador Principal Mafalda Calheiros, estudante do ICBAS.

O estudo foi previamente analisado pela Comissão de Ética CHUPorto|ICBAS, pela Direção do Departamento de Ensino, Formação e Investigação do CHUPorto e pelo Presidente do Conselho de Administração, tendo obtido parecer favorável.

Cumprimentos,

CONSELHO DE ADMINISTRAÇÃO
09/03/2021
Dr. PAULO BARBOSA — Presidente
Dr.ª [illegible] — Vogal Executiva
Prof. Doutor JOSÉ BARROS — Diretor Clínico
Dr.ª RITA VELOSO — Vogal Executiva
Enf.º EDUARDO ALVES — Enfermeiro Diretor

* Em todas as eventuais comunicações posteriores sobre este estudo é indispensável indicar a nossa ref.ª.

REPÚBLICA PORTUGUESA
SAÚDE

SNS SERVIÇO NACIONAL DE SAÚDE

centro hospitalar do Porto

APRECIAÇÃO E PARECER PARA A REALIZAÇÃO DE **MIM - CASO CLÍNICO**

Título: **"Congenital disorders of the corpus callosum and development during postnatal life: a case report and review of the literature"**		Ref.ª: **2021.335 (CC-DEFI/288-CE)**
		Investigador: **Mafalda Calheiros** **Estudante do ICBAS**

DIREÇÃO DE ENFERMAGEM:	**PRESIDENTE DO CONSELHO DE ADMINISTRAÇÃO:**
☒ **NÃO SE APLICA**	☑ **PARECER FAVORÁVEL**
☐ **PARECER FAVORÁVEL**	☐ **PARECER NÃO FAVORÁVEL**
☐ **PARECER NÃO FAVORÁVEL**	
Data:	Data: 07 MAR. 2022
	Dr. PAULO BARBOSA Presidente do Conselho de Administração do CHUP

PARECER FAVORÁVEL

07 MAR. 2022

Dr. SEVERO TORRES
Assessor do Presidente do Conselho de Administração

Em conformidade. Pode ser autorizado.

Prof.ª Doutora Luísa Lobato
Diretora do DEFI

04/03/2022

Luísa Lobato
Diretora do DEFI

Resumo das avaliações dos Intervenientes no Circuito de Submissão dos Estudos de Investigação

	Parecer	Data
Serviço de Investigação Clínica	NA	
Comissão de Ética CHUP|ICBAS	Favorável	15/12/2021
Encarregada da Proteção de Dados (EPD)	NA	
Responsável pelo Acesso à Informação (RAI)	Deferido	02/03/2022
Direção do DEFI	Pode ser autorizado	03/03/2022

CC

REPÚBLICA PORTUGUESA SAÚDE | SNS SERVIÇO NACIONAL DE SAÚDE | centro hospitalar do Porto | U.PORTO

COMISSÃO DE ÉTICA CHUPorto / ICBAS

APRECIAÇÃO E VOTAÇÃO DO PARECER

Deliberação	Data: 15/12/2021	Órgão: Reunião Plenária

Título: **"Congenital disorders of the corpus callosum and development during postnatal life: a case report and review of the literature"**		Ref.ª: **2021.335 (CC-DEFI/288-CE)**
Protocolo/Versão: **CC**	Promotor: **o(a) próprio(a)**	Investigador / Local: **Mafalda Calheiros** **S. de Obstetrícia - CHUPorto**

A Comissão de Ética CHUPorto / ICBAS, ao abrigo do disposto no Decreto-Lei n.º 80/2018, de 15 de Outubro, em reunião realizada nesta data, apreciou a fundamentação do relator sobre o pedido de parecer para a realização do **CC** acima referenciado:

Ouvido o Relator, o processo foi votado pelos Membros da Comissão de Ética CHUPorto / ICBAS presentes:

Presidente: Prof. Doutor João Nuno Melo Beirão
Vice-Presidente: Dr.ª Paulina Aguiar

~~Dr. Aníbal Albuquerque, Prof.ª Doutora Carla Teixeira,~~ Dr.ª Cármen de Carvalho, Dr.ª Fernanda Manuela Costa, Dr. Gonçalo Senra, ~~Prof. Doutor José António Pinho, Prof.ª Doutora Margarida Araújo,~~ Prof.ª Doutora Maria Strecht, Prof.ª Doutora Susana Magalhães.

Resultado da votação:

PARECER FAVORÁVEL

A deliberação foi aprovada por unanimidade.

Pelo que se submete à consideração superior.

Data 15/12/2021

O Presidente da Comissão de Ética CHUPorto / ICBAS

Prof. Doutor João Nuno Melo Beirão

Imp.10/2019

INSTITUTO DE **CIÊNCIAS BIOMÉDICAS ABEL SALAZAR**