Neuropsychological Performance in Tetralogy of Fallot: A Protocol Integrating Genetics, Cognitive Assessment, and Brain and Cardiac Imaging

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Abstract

Introduction: Tetralogy of Fallot (TOF) is the most common form of cyanotic congenital heart disease. Although early surgical repair has increased the survival rates, many clinical and perioperative factors, hypoxemia in particular, seem to be associated with impaired neuropsychological outcomes, such as inattention and dysexecutive function; however, it is unclear whether this outcome is secondary to cerebral damage. A current gap in this field is the correlation between morphofunctional brain changes (including insults occurring from intrauterine to late postoperative development) and cognitive function.

Objective: To investigate if genetic, clinical factors, brain, and cardiac morphofunctional changes can predict neuropsychological performance.

Methods: We used a theoretical directed acyclic graph to investigate potential factors impacting neuropsychological performance in TOF patients. Patients and matched controls will undergo neuropsychological testing and behavior questionnaires. In contrast, TOF patients will be evaluated with genetic-molecular exams and advanced cardiac and brain magnetic resonance image examinations to assess structural and functional brain changes.

Conclusion: Through a comprehensive evaluation encompassing brain and cardiac morphofunctional changes, genetic factors, and cognitive performance, we expect to improve our understanding of the neuropsychological profile of patients with TOF. This innovative approach includes the genetic-molecular evaluation, and a control group matched for main environmental factors. This strategy holds the potential to significantly enhance our understanding of the neurodevelopment of patients with TOF, thereby paving the way for improvements in cardiological and pediatric care.

Introduction

Congenital heart defects (CHDs) are malformations of the cardiovascular system with epidemiological importance due to their significant incidence (8/1,000 live births) (Gaynor et al., 2010). These malformations range from mild anatomical changes with low clinical and hemodynamic impacts to complex CHDs, such as cyanotic ones (Bailliard & Anderson, 2009). Tetralogy of Fallot (TOF) is the most common cyanotic CHD, accounting for approximately 7–10% of all CHDs (Kordopati-Zilou et al., 2022). Patients with TOF present with varying degrees of chronic hypoxemia until corrective surgery is performed, preferably in the first year of life (Bailliard & Anderson, 2009).

The advent of surgical correction for TOF has significantly impacted the longevity of patients with this condition; the 25-year survival rate exceeds 90% (Kordopati-Zilou et al., 2022). This increased longevity, however, has been accompanied by neurodevelopmental changes often associated with perioperative factors, early-life hypoxemia, and even intrauterine factors (Bellinger et al., 2015; Hövels-Gürich et al., 2006; Kordopati-Zilou et al., 2022; Mor-

ton et al., 2021).

An increased prevalence of psychiatric disorders such as anxiety, depression, bipolar disorders, sleep disorders, and Attention Deficit Hyperactivity Disorder (ADHD) has been identified in patients with TOF (Czobor et al., 2021; Holland et al., 2017; Holst et al., 2020; Hsu et al., 2021). However, genetic and clinical heterogeneity has impacted the interpretation of findings from previous studies. In addition, cultural and socioeconomic factors affect brain development and could increase the prevalence of psychiatric disorders in these patients (Favilla et al., 2021; Kordopati-Zilou et al., 2022). To our knowledge, there is no previous systematic exploration of the associations between neurodevelopmental issues and hemodynamic changes in the late postoperative period in patients with TOF.

In neurodevelopmental studies, brain morphological imaging characteristics of patients with TOF frequently do not correlate well with neuropsychological outcomes (Bellinger et al., 2015; Holland et al., 2017), possibly due to the clinical heterogeneity imposed by anatomical cardiac differences of the evaluated subjects. Advanced (e.g., functional) brain magnetic resonance imaging (MRI) modalities appear to be promising for such correlation, like identifying a correlation between right-hemispheric sulcal patterning and executive function in patients with TOF (Morton et al., 2021). These advanced techniques may be essential to fully understand the relationships between these patients' brain abnormalities and neurodevelopmental outcomes (Holland et al., 2017).

Thus, the present proposal entails a comprehensive assessment of the cognitive profile of patients with TOF using neuropsychological testing, genetic evaluation, advanced cardiac imaging, and neuroimaging methods, including cardiac four-dimensional (4D) flow and brain functional resonance imaging, to disentangle the contribution of those factors.

Materials and Methods

Study Design

This cohort study will include consecutive patients with TOF referred from cardiology outpatient clinics and Rede D'Or hospitals. Patients' medical records will be accessed to evaluate inclusion and exclusion criteria. All eligible, consenting patients will be enrolled; clinical data will be extracted from their medical records, including the need for reoperation, postoperative complications, and palliative surgery before a significant correction. Online screening consultations will be performed to explain the study design and to invite matched

controls (below). Finally, participants will undergo a cross-sectional analysis, including neuropsychological assessment, brain and cardiac MRI examinations, genetic-molecular evaluation, and quality-of-life questionnaires.

Search Subjects

Patients with TOF from the cohort study will be selected for the neurodevelopmental study based on the inclusion criteria of age 7–18 years and having undergone corrective surgery. Patients with formal contraindications to MRI (e.g., pregnancy and claustrophobia), previous diagnoses of genetic syndromes and associated severe cardiac malformations (e.g., atrioventricular septal defect, double-outlet right ventricle, and pulmonary atresia), and those with brain injuries unrelated to TOF (e.g., trauma, tumor, and brain infection) will be excluded.

For the neurodevelopmental control group, patients with the same socioeconomic and cultural background as the patients, such as family members, neighbors, and schoolmates of similar age, will be identified during the consultation with the patient's parents and invited to participate. Individuals with medical histories of congenital heart disease, neuropsychiatric disease, severe systemic disease, traumatic brain injury requiring hospitalization, major surgical procedures, and intensive care unit hospitalization with the need for mechanical ventilatory support for any reason will be excluded from the control group.

Study Procedures

Neuropsychological evaluation:

An experienced neuropsychologist will administer the neuropsychological examinations following standard recommendations. The following evaluation instruments will be used: the coherence and inference test (Carvalho, 2014) [pragmatic language], Wechsler Abbreviated Scale of Intelligence (Wechsler, 2014) [intelligence], d2-R test of attention (Araujo, 2016) [attention], five digits test (Paula & Malloy-Diniz, 2015) [executive functions], Nine Hole Peg test (de Lala & Cardoso, 2022) [motor dexterity], Rey Auditory Verbal Learning Test [verbal memory], Benton Visual Retention Test (Salles et al., 2016) [visual memory], School Achievement Test II (Sartori, 2017) [academic achievement], and Corsi Block Tapping test (Galera & Souza, 2010).

Questionnaires will also be used for neuropsychological evaluation. Experienced and trained physicians will administer the Vineland Adaptive Behavior Scales 3 (Vineland-3) (Pepperdine & Mc-

Crimmon, 2018) to assess daily living functionality. Participants or their guardians (as recommended for each instrument) will fill out the following questionnaires with the supervision of a physician: the Children's Depression Inventory (CDI) (Cruvinel et al., 2008) [depression]; Swanson et al. scale for the evaluation of the symptoms of ADHD IV (Mattos et al., 2006) [ADHD]; Screen for Child Anxiety Related Disorders (SCARED) (Barbosa et al., 2002) [anxiety]; and Social Responsiveness Scale 2 (SRS-2) (Constantino & Scale, 2012) [Autism Spectrum Disorder].

Brain MRI:
The protocol comprises acquiring T1 and T2-weighted volumetric structural image sequences with high anatomical resolution and multi-shell diffusion images with high angular resolution). The acquisition protocol includes the following:
1. Automated positioning for the location of brain structures (auto-brain localizer).
2. Anatomical images with the following multiplanar pulse sequences: T1 and T2-weighted volumetric sequences, with isotropic voxel of 0.8 mm resolution, T2-weighted spin-echo turbo, and FLAIR.
Diffusion protocol was acquired using a multi-shell sequence: diffusion gradients were applied in 30 and 64 directions with three diffusion weighting factors (b = 0, b = 1000, b = 3000 sec/mm²). The images will be post-processed through a standard processing pipeline and the software MRtrix, DSIStudio, and SIEMENS Syngo via reconstruction software.

Brain Image Processing:
The acquired neuroimaging data will be structured and organized following the Brain Imaging Data Structure (BIDS) protocol, which allows for standardization in the organization of the files and the description of data sets. This allows the data to be used and shared among researchers (Gorgolewski et al., 2016). The processing software and the data storage database used in the project will be compatible with the BIDS [BIDS-Apps] (Gorgolewski et al., 2017).

Optimized use of data processing and analysis software is possible when the metadata needed for analysis (e.g., task details or imaging protocol) is easily accessible and standardized. The development of automated tools to verify the consistency and integrity of data sets allows fully automated analysis workflows to be applied, significantly increasing reproducibility and analysis efficiency.

Some computational tools, such as the FSL (FMRIB Software Library v.5.0) package, MRtrix, and DSI Studio (http://dsi-studio.labsolver.org), will be used together.

Genetic-molecular investigation:
Genomic DNA will be extracted from peripheral blood samples collected in EDTA-treated tubes using standard automated protocols in the QIAsymphony instrument. After fluorometric quantification, 500 ng of genomic DNA will be used for library preparation using the Illumina DNA PCR-Free Prep kit, according to the manufacturer's instructions. Libraries will be run in a NovaSeq X Plus Sequencing System using 10B or 25B flow cells. After demultiplexing, FASTQ files will be aligned to the human reference genome hg38, and variants will be called using a DRAGEN server onboard the sequencing system. VCF files, including SNVs, indels, CNVs, and structural variants, will be loaded to Emedgene software for tertiary analysis.

Cardiac MRI:
Patients will undergo cardiac MRI examinations on a 3-Tesla device with 4D flow capabilities (MAGNETOM Prisma; Siemens et al.). Black blood–type sequences will be used for anatomical evaluation. Cine-MRI-type images will be acquired for anatomical and functional evaluation using gradient-echo pulse (balanced turbo field echo—SSPF) sequences (Sakuma et al., 1993). Late enhancement images will be acquired for the characterization of focal myocardial fibrosis (Kim et al., 1999).

T1 mapping images will be acquired with a modified Look-Locker inversion recovery sequence using single-shot steady-state free precession readouts before and after administering 0.2 mmol/kg gadolinium. Additionally, a 2-cm² circular region of interest will be defined at the center of the left ventricle on T1 maps to obtain the pre- and post-contrast blood pool values required for calculating the extracellular volume. Images will be acquired with a three-dimensional phase contrast sequence with three-dimensional velocity encoding (RM 4D flow) to evaluate intracardiac flows, the aorta, the pulmonary arteries, the venous circulation, and palliative shunts (Dyverfeldt et al., 2015).

The examination data will be stored on hard drives in Digital Imaging Communications in Medicine (DICOM) format. The images will be analyzed using multiplatform commercial software [OsiriX MD (Pixmeo) and Circle cardiovascular imaging 42].

Quality of Life Assessment:
The Kidscreen Quality of Life questionnaire is a validated tool for the Brazilian population (Guedes & Guedes, 2011). It will allow us to assess the impacts of neurodevelopment impairments and TOF on patients' quality of life.

Data Collection from Medical Records

Data will be collected from medical records and entered into electronic case-report forms using the Research Electronic Data Capture platform (Vanderbilt University, Nashville, TN, USA). Data in the following main domains will be recorded: past and current diagnoses, presurgical status, major surgery data, short-term and long-term postoperative evaluation data, reoperation data (where appropriate), and current cardiac and neurologic clinical data.

Outcome Variables

The primary outcome examined in this study will be participants' neuropsychological performance, determined from neuropsychological test results. Secondary outcomes will be evaluated using behavioral questionnaire (CDI, SCARED, SRS-2, and Vineland-3) results, brain MRI findings, cardiac MRI results (including ventricular function, fibrosis, and hemodynamic findings from 4D flow sequences), and Kidscreen quality of life questionnaire results.

Prediction of Covariates and Confounders

To address potential influences on the correlation between the primary exposure (TOF) and primary outcome (neuropsychological performance), potential covariates, mediators, and confounding variables have been selected based on a theoretical framework using a directed acyclic graph (Figure 1). This framework will allow us to build a multivariate regression model for these potential predictors and confounding variables. Only genetic factors were considered potential ancestors of both the exposure and outcome; thus, genetic factors will be considered a potential confounder of our model. Hypoxemia, arrhythmia, and surgery will be considered mediators of the relationship between the exposure and outcome. Thus, including these factors in the final statistical model to establish the direct and indirect effects of these variables is highly recommended.

In the same way, variables related to surgery, such as the aortic clamp time, cardiac bypass time, postoperative stroke, and postoperative convulsion, can influence the outcome. All those covariates will be included in the statistical model. On the other hand, although such factors are included in the theoretical framework, patients with prematurity and neurological lesions unrelated to TOF will be excluded; a matched control group will be used to control for age, socioeconomic status, and educational level.

Statistical Plan

Correlations of imaging and cognitive findings with clinical, hemodynamic, perioperative, and genetic factors will be examined. The descriptive analysis of the data will consist of the estimation of means or medians (with standard deviations or interquartile ranges) for numerical variables and the calculation of percentages (numbers of observations) for categorical variables. Skewness and kurtosis tests will be used to analyze the distributions of variables, which may be transformed (using a logarithmic function) if deviation from normality is detected. The variables of interest will be compared between groups using multivariate linear or logistic regression models; the association between study variables will be examined using the same methods. The statistical tests will be performed using SPSS (version 24.0; IBM Corporation, Armonk, NY, USA), and a 5% significance level will be used.

Sample Size Determination

The sample size was estimated using inattention in patients with TOF, the best-studied endpoint (Holst et al., 2020). We determined that a sample of 78 participants (1:1 group ratio) will be needed, considering an alpha level of 0.05, a power of 80%, and a difference between mean Attention Deficit/Hyperactivity Disorder Rating Scale Inattention subscale scores of 3.9, with standard deviations of 4.1 for the control group and 7.5 for patients with TOF.

Attrition rates are expected to be high in studies involving the neuropsychological assessment of pediatric patients (Stets et al., 2012), although they vary widely in observational cohort and long-term intervention studies (Sindhu et al., 2019; Zebracki et al., 2003). Considering this point, we considered an attrition rate of 29% in the sample size calculation (Zebracki et al., 2003), leading to a final sample of 100 participants (50/group).

Ethical Considerations

Institutional and national ethics committees have approved this protocol (#CAAE 24361619.9.0000.5249), which will be implemented in accordance with World Health Organization recommendations and the Declaration of Helsinki. The main study procedures will be presented to participants and their legal representatives.

The identities of the subjects will be kept confidential. Researchers and collaborators will be responsible
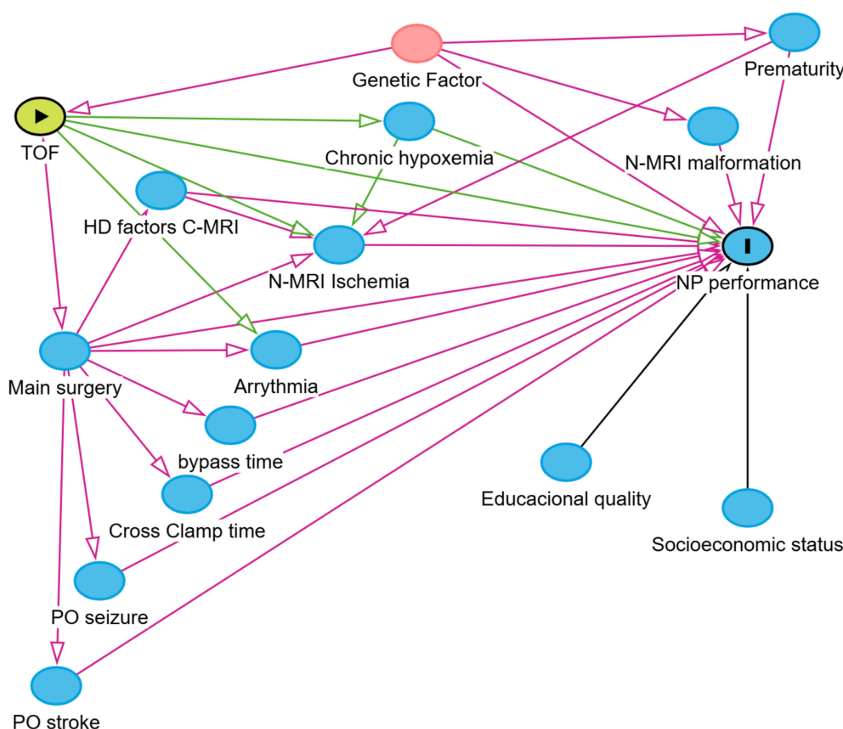
Figure 1: *Predictors of the neuropsychological performance of patients with tetralogy of Fallot. TOF, tetralogy of Fallot; N-MRI, neurological magnetic resonance imaging; HD, hemodynamic; C-MRI, cardiac magnetic resonance imaging; NP, neuropsychological; PO, postoperative (within 48 h after surgery). Arrow colors: green, causal path; pink, biasing path; black, path non-associated with the main causality one.*

for collecting the data, which will be used only for research purposes, and maintaining its confidentiality.

The ethics committee has also approved the informed consent form and its application, which will follow the rules of good clinical practice. The subjects will be aware that their participation is voluntary, and refusing to participate will not influence patients' medical follow-up.

Discussion

Although many patients with TOF survive into adulthood, a significant number experience learning difficulties due to neuropsychological impairment. Research on this subject, particularly in Brazil, is limited.

The present study aims to investigate and disentangle the impact of morphofunctional brain and cardiac changes, genetic profiles, and clinical factors on the neuropsychological performance of patients with TOF in Brazil. By excluding patients with genetic syndrome phenotypes and severe forms of the disease, such as those presenting with pulmonary atresia, we aim to identify hemodynamic and perioperative factors that impact the brain development of patients with the classic form of TOF.

In addition, we will include matched controls to minimize the possible influences of sociocultural factors. Besides this, patients with congenital heart disease may present with genetic syndromes without classic phenotypic signs with impairments to the performance on neuropsychological tests (Kordopati-Zilou et al., 2022). Therefore, the genome analysis will allow us to detect these unknown genetic syndromes. This is the first time a deep genomic analysis will be done in neurodevelopment studies involving patients with TOF. Although neurological changes in patients with TOF are known to be multifactorial, with intrauterine events, chronic hypoxemia, and perioperative factors contributing, a better understanding of structural and functional brain and cardiac changes in these patients and their relationships to neuropsychological disorders may contribute to the development of diagnostic tools to aid rehabilitation (Kordopati-Zilou et al., 2022). In addition, understanding the impacts of genetic factors, hemodynamic changes (as assessed by MRI with 4D flow), and perioperative factors on these changes and relationships can provide new insights aiding the prevention of neurodevelopmental issues.

In this protocol, the authors will address several issues inherent to observational studies to avoid bias using a theoretical directed acyclic graph. A comprehensive assessment including neuropsychologi-

cal tests, genetic-molecular exams, advanced cardiac and brain magnetic resonance image examinations, and the inclusion of carefully matched controls are the main strengths of the protocol. Some limitations must be recognized, such as using a convenience sample. Nevertheless, including all consecutive patients who met the inclusion/exclusion criteria may reduce the risk of a significant sampling bias. The knowledge acquired with this study may aid the future development of cardiological approaches that reduce the impacts of those various factors involved in the neurodevelopment of patients with TOF through the application of preventive measures from the neonatal period, including the perioperative period and the monitoring, diagnosis, and, eventually, early treatment of psychiatric and neurodevelopmental issues that arise.

Funding

Conflicts of Interest

The authors declare no conflict of interest.

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