INPLASY PROTOCOL

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None declared.

Brain morphofunctional changes associated with pain in children, adolescents and young adults with sickle cell disease

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Review question / Objective: **Understanding of brain morphofunctional changes in children, adolescents and young adults with Sickle cell disease.**
Eligibility criteria: **Studies were included in the current systematic review if they met each of the following eligibility criteria: a) they included children (0 -9 years), adolescents(10-19 years old) , young adults (20-24 years old) and young adults (25-29 years old) with SCD following the WHO classification criteria; b) examined pain intensity/ frequency/duration and/or functional impairment of pain; c) examined brain connectivity; d) examined brain thickness e) were quantitative studies; f) use magnetic resonance imaging, functional magnetic resonance imaging, electro-encephalography, transcranial Doppler ultrasound, and magnetic resonance angiography as evaluation measures.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 05 December 2022 and was last updated on 05 December 2022 (registration number INPLASY2022120022).

INTRODUCTION

Review question / Objective: **Understanding of brain morphofunctional changes in children, adolescents and young adults with Sickle cell disease.**

Rationale: **Sickle cell disease (SCD) is multisystemic and debilitating. In it, the hemoglobin gene presents a mutation that causes an abnormal polymerization of the red blood cells, making them sickle-shaped. This structural feature facilitates blood vessel obstruction, causing vaso-occlusive crises that impair oxygen supply to organs and viscera, resulting in neuroimmune and neurovascular disorders associated with target organ damage and recurrent acute pain and chronic pain (Pecker , 2021) .**
The definition revised by the International Association for the Study of Pain (IASP)

conceptualizes pain as “an unpleasant sensory and emotional experience associated, or similar to that associated, with a real or potential tissue injury” (Raja et al , 2020) . Most children with SCD experience at least one pain crisis/year and these crises have significant negative impacts (Reeves et al, 2019). The presence of long-term pain can affect global brain activity (Case et al , 2019) . The lack of inhibitory control in the dorsal horn of the spinal cord, both due to local and supraspinal dysfunction, causes phenotypic alteration of Aβ fibers specialized in conducting non-painful stimuli, favoring central sensitization .

The existing literature supports a model in which brain maturation occurs along a hierarchical organizational axis. This evolutionary process is accompanied by patterns of cortical expansion with brain regions presenting additional functional gains accompanied by an increase in cortex thickness, having its peak between 9 and 12 years of age and, later, stabilizing or presenting a decline (Sydnor,2021) . The presence of a painful condition since childhood, as is characteristic of SCD, probably generates long-term effects that can affect brain activity as a whole, including the brain networks that are necessary for the performance of the entire set of functions possible to an individual. human being (Pecker,2021) . The central sensitization of multiple structures caused by pain episodes can lead to a maladaptive change in important anatomical/functional networks that process information in all dimensions of pain, that is, sensorial, emotional and cognitive (Lopes et al , 2022), leading to a increased vulnerability to injuries (Farrell et al, 2019).

Pediatric imaging tests can identify patients at high risk for CNS disease progression in young adulthood (Champlin et al , 2021) . The use of EEG to assess brain function abnormalities and establish a brain pain marker is attractive because it is safe, not invasive, widely available and potentially mobile (McVoy et al, 2019) with low spatial resolution as a weakness, resulting in a low signal from deeper brain structures (Farrell et al , 2019) . In vivo magnetic resonance imaging allows the quantification of the macroscopic properties of cortical structures, having functional magnetic resonance imaging as specificity, which has the ability to detect variations in blood flow in response to neuronal activity through the BOLD (Blood Oxygenation Level Dependent) effect. In a resting state, space-time capacity can be assessed and deeper brain structures and networks can be identified with high spatial resolution (McCarty et al , 2021).

Resting-state functional connectivity (RFC) studies of brain activity are increasingly being used to study chronic pain conditions. RFC involves correlating the time course of MRI BOLD signal changes between various brain regions. In the absence of external stimuli, this resting state activity provides a view of functionally interconnected brain networks while patients are at rest, which is ideal for the assessment of ongoing spontaneous clinical pain (Darbari et al, 2015) identifying patients at high risk for progression of SCD in the CNS in young adults and encouraging complementary therapies and/or more aggressive treatments (Brandow et al, 2018) .

Condition being studied: Sickle cell disease (SCD) is a genetic hemoglobinopathy resulting from a mutation in the β-globin gene characterized by hemolytic anemia, vaso-occlusive pain and progressive organ failure. Vaso-occlusion is a multifactorial process involving the occlusion of small blood vessels by sickled red blood cells (RBCs), polymorphonuclear neutrophils, platelets, and activated endothelial cells. This occlusive process leads to hypoxia and then to ischemia, which is associated with local inflammation and pain (Lopes et al , 2022) . Most children with sickle cell disease experience at least one pain crisis per year, and these have significant negative impacts, such as poor quality of life, more frequent absences from school, depression and damaged relationships (Saramba et al,2020). Pain is defined as an unpleasant sensory and emotional experience associated, or similar to that associated, with a real or potential tissue injury” (Raja et al ,2020) . In FD it can be acute, chronic, but often episodes of acute

pain occur in the presence of chronic pain. A recent expert consensus suggests subdividing chronic pain in SCD into that associated with another identifiable cause, or that without an identified cause (Cançado , 2007).

Acute pain episodes are abrupt in onset, unpredictable and account for the highest number of admissions to emergency services, although these episodes are often managed at home (8) . Acute pain episodes increase in frequency with age, and a chronic pain syndrome develops in 30% to 40% of adolescents and adults with SCD (Brandow , 2018). Chronic pain involves several neuronal plasticity processes that have not yet been decoded in terms of involvement of specific circuits and cause-effect relationship (Farrell ,2019) . An important feature of chronic pain is its sustained nature, which may involve brain regions related to cognitive and affective coping responses, in addition to sensory-discriminatory processes (Friedrichsdorf ,2020) . There is a consensus based on imaging studies that the origin of the painful sensation is not restricted to a single area, but that pain results from the integration of brain areas, forming specific brain networks (Darbari, 2015). Human studies of brain networks, or brain connectivity, began in the 1990s with the development of structural and functional techniques such as tractography (Bhatt et al, 2020) and fMRI (McCarty et al, 2021).

The results of previous studies suggest that pain in children is associated with structural changes in the gray matter and that the magnitude of these structural changes is associated with the duration of pain (Bhatt et al ,2020). Several brain regions must be involved, such as posterior and anterior cingulate cortex, medial prefrontal cortex, precuneus, lateral temporal lobe, hippocampus, parahippocampus, medial prefrontal cortex and insula. Furthermore, specific networks may be involved, such as the emotion regulation network (ERN), the sensorimotor network (SMN), and the default mode network (DMN) (Champlin et al, 2021). However, categorizing patients just by having pain is too general, as each pain condition and associated factor can strongly influence brain imaging. Previous studies have investigated brain alterations associated with FD pain in general (Bhatt et al,2020), (Colombatti et al , 2016), (Case et al , 2017),(Darbari et al , 2015),(Zempsky et al, 2017).

METHODS

Search strategy: A systematic review of the literature will be carried out in PubMed, Latin American and Caribbean Literature in Health Sciences (LILACS) and Scientific Electronic databases. Library Online (SciELO). In addition, a manual search will be performed by two reviewers in the references of the included studies. There will be no date or language limitation. The following descriptors will be used: sickle cell disease, child, brain connectivity, functional connectivity, pain.

Participant or population: Studies will be included in the current systematic review if they meet each of the following eligibility criteria: a) have included children (0 -9 years), adolescents(10-19 years) , young adults (20-24 years) and young adults (25-29 years) with SCD.

Intervention: Electroencephalogram and magnetic resonance and BOLD.

Comparator: Differences in brain regions related to pain processing between the control groups and the group of children, adolescents and young adults with sickle cell disease in relation to connectivity and cortical thickness.

Study designs to be included: The search and analysis of the articles will be carried out independently by two reviewers. After the titles and abstracts of the studies are evaluated, those that do not meet the eligibility criteria will be excluded, with disagreements resolved by a third reviewer. Studies that meet the predetermined criteria will have their full text acquired for detailed analysis and data extraction.

Eligibility criteria: Studies were included in the current systematic review if they met each of the following eligibility criteria: a) they included children (0 -9 years),

adolescents(10-19 years old) , young adults (20-24 years old) and young adults (25-29 years old) with SCD following the WHO classification criteria; b) examined pain intensity/frequency/duration and/or functional impairment of pain; c) examined brain connectivity; d) examined brain thickness e) were quantitative studies; f) use magnetic resonance imaging, functional magnetic resonance imaging, electroencephalography, transcranial Doppler ultrasound, and magnetic resonance angiography as evaluation measures.

Information sources: PubMed, Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) e Scientific Electronic. Library Online (SciELO).

Main outcome(s): The results of cross-sectional studies show a decrease in cortical thickness and an increase in functional connectivity mainly concentrated in the precuneus and anterior cingulate cortex, regions that make up the Default Mode Network (DMN) and/or the Pro-nociceptive Network. These alterations correlate with the frequency of pain and hospitalizations and the increased connectivity in structures of the Antinociceptive Network is associated with a decrease in the frequency of pain crises and their consequences.

Data management: An electronic data extraction file was created to organize the relevant extracted data from each study. The extracted data pertains to the demographics of the participants, as well as the evaluated variables and the measures used.

Quality assessment / Risk of bias analysis: To assess the risk of bias, the selected articles were analyzed following the Newcastle-Ottawa Scale with an assessment of eight items, categorized into three groups: 1) selection of study groups; 2) comparability of groups and; 3) verification of the outcome of interest. The scale score ranges from four (minimum) to nine (maximum).

Strategy of data synthesis: In the current review we identified brain regions that showed significant functional or structural changes in patients compared to control participants, or within patients between affected and unaffected sites. The reported brain regions were categorized into 14 regions of interest (ROIs) that are associated in previous studies with pain processing: anterior cingulate cortex, posterior cingulate cortex, ventromedial frontal cortex, insular cortex, primary motor cortex, right primary somatosensory cortex, subcortical pattern mode network, supratemporal gyrus, parahippocampus, right precuneus, posterior precuneus, medial prefrontal region, right prefrontal region, posterior calcarine region .

Subgroup analysis: Categorization was performed separately for positive changes (eg, increased BOLD activity vs. control subjects) and negative changes (eg, decreased BOLD activity in patients vs. control subjects)/EEG (areas with increased connectivity versus areas with decreased of connectivity).

Sensitivity analysis: a) Including or excluding studies that showed some ambiguity in their inclusion criteria

Language restriction: English.

Country(ies) involved: Brazil.

Keywords: Sickle Cell Disorders; pain; children.

Contributions of each author:

Author 1 - Carla Marques - Study design; Data collect; Analysis / Interpretation of data; Involvement in the preparation of the manuscript; Responsibility for the accuracy and completeness of all aspects of the research.
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