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Examining Benefits of Early Intervention in Cases of Pediatric Chronic Hypoxia

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Examining Benefits of Early Intervention in Cases of Pediatric Chronic Hypoxia

by

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Abstract

There is a strong foundation of evidence and consensus in the literature that hypoxia has adverse impacts on brain function. Recent research has broadened the field in two directions. One is the treatment for acute hypoxic injuries, and the second is regarding the accumulative impact of intermittent or chronic hypoxia. Historically, in cases of acute hypoxia, action is taken to remedy the source of hypoxia. Physical and cognitive rehabilitation has typically been provided as needed depending on the severity of the injury. While cases of intermittent or chronic hypoxia may not demonstrate an acute urgency for treatment and rehabilitation, current research shows that the long-term impact can be just as damaging to cognitive, behavioral, psychosocial, and physical development. However, since the adverse impacts are slowly accumulating over the course of a chronic hypoxic condition, opportunities for intervention can be missed. Often the chronic state is considered secondary to the catalyst disease or event that demands primary focus, and the impacts of hypoxia are often relinquished to the plasticity of the brain for self-moderation.

This paper looks at the causes, diagnoses, treatments, opportunities, and benefits of early and sustainable interventions.

Keywords: Hypoxic-impact, early intervention, cognition, psychosocial development, life-satisfaction.

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EXAMINING BENEFITS OF EARLY INTERVENTION IN CASES OF PEDIATRIC CHRONIC HYPOXIA

Introduction

Hypoxia is when oxygen is not available in sufficient amounts to tissues in order to maintain homeostasis (Bhutta et al., 2022). This can be attributed to biochemical insufficiency with low levels of blood oxygen resulting in hypoxemia, such as in anemia or where cells cannot bind and transport oxygen to tissues. Another contributing factor can be mechanical, where blood flow is inhibited, resulting in ischemia. Ischemia can be primary direct - cardiac insufficiency, primary indirect – venous insufficiency, or secondary direct - as in a cerebral vascular accident or secondary indirect - as in cardiopulmonary bypass procedures. (Bhutta et al., 2022)

O'Dougherty et al., (1985) was one of the first foundational research projects on children with a cyanotic congenital heart defect to assess the impact of chronic hypoxia. The authors referenced eight markers: neurologic examination, visual evoked response, EEG, behavioral adjustment, cognitive, perceptual-motor, and attentional functioning, and school performance. On outcome evaluation, these children evidenced diverse neurophysiologic dysfunction. Chronic hypoxia was associated with impaired motor function, inability to sustain attention, and low academic achievement. Often referenced by subsequent literature, great strides have been made to identify causation, methods of diagnosis, and potential interventions. As we move forward in this area to align opportunities of diagnosis and timing of interventions, the question arises would children with a diagnosed chronic state of hypoxia benefit from *early* assessment, treatments, and interventions to support or mitigate the adverse impacts to cognitive, motor skills, and social development?

Causes

The first step in understanding the foundational question of the impacts of hypoxia on developmental stages, both cognitive and physiological, is to take an in-depth look at the etiologies and presentation of hypoxia in the patient population. Bhutta et al. (2022) made a detailed evaluation of the two main etiologies for hypoxia and presented them as low blood flow to the tissue, or low oxygen content in the blood (hypoxemia), then further broken down into four pathophysiologies as follows:

1. **Hypoventilation** - Airway obstruction- ie. COPD, Impaired respiratory drive - i.e., sedation or coma, Restricted movement of the chest wall - i.e., ankylosing spondylitis, Neuromuscular diseases- i.e., muscular dystrophy, amyotrophic lateral sclerosis, or phrenic nerve injuries.
2. **Ventilation-Perfusion Mismatch (V/Q Mismatch)** - impairing the ventilation and therefore decrease the ratio of ventilation to perfusion, or increased ventilation where the surface area available for gas exchange is decreased, which causes higher ventilation in comparison to perfusion leading to a high V/Q ratio.
3. **Right to Left Shunt** - The blood crosses from the right to the left side of the heart without being oxygenated.
4. **Impaired Diffusion of Oxygen** - Oxygen diffusion is impaired between the alveolus and the pulmonary capillaries. Causes are usually interstitial edema, interstitial inflammation, or fibrosis.

Bhutta et al., (2022) goes on to break down these etiologies into four diagnostic groups that can be deemed acute, intermittent, or chronic. They are as follows:

1. **Hypoxemic Hypoxia**- Low oxygen tension in the arterial blood (PaO₂) is due to the inability of the lungs to properly oxygenate the blood.
2. **Circulatory Hypoxia** - It is due to pump failure
3. **Anemic Hypoxia** - It is because of a decrease in oxygen-carrying capacity due to low hemoglobin, leading to inadequate oxygen delivery.
4. **Histotoxic Hypoxia (Dysoxia)** - Cells are unable to utilize oxygen effectively (2022).

Regardless of the point of origin, both intermittent or chronic hypoxia has a well-documented impact on cognitive, motor skill, and social function development in both children and adults (O'Dougherty 1985, Nyakas 1996, Michiels 2004, McMorris 2017, Brownlee

2020, Pieolva 2021). DiFiore et al. (2021) and Giannopoulou et al. (2018) further distinguished measurable impact to memory, executive function, fine and gross motor skills acquisition, and psychological pathologies including: depression, ADHD, anxiety, and OCD as long-term issues. Understanding the etiologies of hypoxia is valuable for this paper in that it demonstrates multiple disciplines could be engaged with the patient in determining diagnosis, treatment strategies, and to help project long-term outcomes.

Diagnosis

According to the Cleveland Clinic, diagnosis of hypoxia typically focuses on immediate treatment to mitigate the underlying cause of the hypoxia. These tests include but are not limited to MRI, fMRI, MRP, PET scan, SPECT scan, T2-FSE, CAT scan, arterial Blood Gas Test, O₂ saturation, V/Q exam, Pulmonary Function test, and Six Minute Walk Test. While these tests accurately identify and measure acute hypoxia, in cases of chronic hypoxia, they are used for monitoring hypoxic stages. Once hypoxia has moved from an acute phase to a chronic phase, additional tests can be used for measuring long-term impacts. These include but are not limited to EEG, neuropsych evaluations, fine motor skills, and gait assessment. Two new promising imaging technologies are Diffusion Tensor Imaging (DTI) and Proton Magnetic Resonance Spectroscopy (MRS), but these are not widely used at this time (Little et al., 2010).

While the literature seems in agreement on the diagnosis, physical intervention, and long-term impacts of chronic hypoxia on developmental delays, there seems to be some disagreement on the timing of intervention for cognitive support. In children because of “brain plasticity” and in adults because of additional contributing factors such as age, medications, and familial history of dementia (Harvard 2014). Even after treatment to resolve or mitigate the root cause of hypoxia, the long-term adverse impacts may remain or even progress (Annals of

Neurology 2005, Dahri 2021). If hypoxia onset was as a neonate or infant, these impacts could result in developmental delays that often persist into adolescence and adulthood that can ultimately represent long-term neurocognitive disabilities. (Berger et al. 2021).

My research goal is to examine current literature to see if there is available evidence to support early diagnosis and intervention in children with chronic hypoxia to mitigate or reduce adverse impacts on cognitive, motor, and psychosocial development. Understanding the impact of hypoxia on developmental stages is imperative for specialists, that often focus on improving the immediate physical well-being of the child, to broaden their long-term objectives with treatment or referrals that include recognition of resulting developmental delays that may not be in their primary focus. (i.e., a cardiologist treating an infant with a congenital heart defect may accept that the correcting surgical intervention of a Glenn procedure results in chronic hypoxia with blood oxygen levels in the 75-85 range as a successful outcome as life has been sustained, without addressing the impact to the patients quality of life.) The disciplines that may benefit from this research include but are not limited to neonatal pediatricians, obstetricians, cardiologists, neurologists, primary care providers, educators, pulmonologists, psychologists, and endocrinologists.

Methodology

This paper will focus on peer-reviewed literature regarding hypoxia from chronic conditions and its impact on the development of both cognitive and motor skills. While studies on this topic have been ongoing since breakthrough research by O'Dougherty et al., (1985), this paper will focus on original research within the last five years, and assess how it contributes to the field of understanding. The references are accessible through an active library link. This paper will be using current literature within the last five years, unless a historical context is

needed and supported by literature older than that, peer-reviewed, and focused on one of three points:

1. Causes, diagnosis, and impacts of hypoxia on developmental stages
2. Treatments, both physical intervention and strategic behavioral modification support
3. The impact of timings for intervention and referrals.

The preferred literature will be human case studies; however, animal studies will be included if they have pertinent contributions.

Literature Review

The data search produced seventy-two articles using keywords: hypoxic impact, early intervention, psychosocial development, treatment of hypoxia, and barriers to treatment. Of the seventy-two articles, twelve met the criteria of empirical research within the last five years. Twenty-six of the articles were outside of the five-year criteria and are not included in the literature review but are used in the discussion to expand or clarify information in the articles reviewed. The literature reviews are grouped into three categories below.

Impact of Hypoxia on Developmental Stages

Impacts on Perinatal to Infant Development

Ehltling et al., (2022) collected information about the timing and impacts hypoxic ischemia can have in a rat model. This was a quantitative study using experimental procedures. MRI scans, behavior testing, statistical analysis, and ELISAs were used to collect data. There was a total of 69 Wistar rat pups, 39 females and 30 males. The results of this study show that the average size of damage or loss of brain tissue differentiated between the sham/control group and the experimental group on average 20% reduction in the hemisphere of the brain impacted

following hypoxic injury. Over time the damage increased by over 50%. The implication of this study was that chronic hypoxia produces an accumulative impact over time. Authors called for more research regarding alternative treatment options for hypoxic-ischemic encephalopathy will need to be developed with fewer side effects.

Impacts on Childhood to Adolescent Development

Brady et al., (2020) determined whether or not children with chronic illness experience the same social challenges or dissatisfaction as their healthy peers. The research design was quantitative, using a longitudinal study of data collected on children born in Avon County from April 1st, 1991, to December 31st, 1992. The study used 68 identifiable data collection points including, questionnaires for participants to self-report and medical chart notes for clinical assessments. 12,776 participants were followed from birth to 18 years. The findings of the study suggest chronic illness adversely impacts, social development in early adolescence and, whether physical or cognitive in nature, leads to increased rates of mental illness. The authors found that the illness directly and/or the mental health impact resulted in higher rates of absenteeism. The practical implication of this is the recommendation that school absenteeism and peer victimization may be key to identifying children at risk.

Berkelbach van der Sprenkel et al., (2021) focused on how chronic illness impacts psychosocial functioning in adolescents. The research design was quantitative research that gathered data through the Dutch 2013 HBSC-Survey. There were 7,168 adolescent participants, both children with chronic illness (973) as well as healthy children (6,195), between the ages of 11 and 16. Informed consent was acquired, and anonymity was guaranteed. The average z-scores were calculated and graphed showing a significant disparity in life satisfaction, psychosomatic health complaints, conduct problems, and peer problems than their healthy peers. The

implications of this study show chronic illness impacts not only mental and physical development but also impacts social development.

Harbinson et al., (2017) compared functional and psychosocial outcomes in patients with hypoxic-ischemic brain injury in people who have had a traumatic brain injury 4-11 years after having a brain injury.. This study was a quantitative study using a retrospective design. Data collection methods were collecting time of admission, discharge for admission, and Functional Independence Measures. Acute Length Of Stay was used initially, and then they were reassessed using the FIM, Disability Rating Scale, Personal Health Questionnaire Depression Scale, and the Mayo Portland Adaptability Inventory 4. There were 22 participants in this study, participant ages were not defined. Eleven of the participants in this study had a traumatic brain injury, and the other 11 had a hypoxic-ischemic brain injury. The results of this study showed that patients who had HIBI had a lower FIM and cognitive score than patients who had a TB, they also had lower scores on the DRS, PHQ-9, and total MPAI-4 at follow-up. To compare functional and psychosocial outcomes of patients with HIBI to those of case-matched patients with TBI 4-11 years after brain insult. This study suggests that patients with HIBI achieve fewer long-term functional improvements compared to patients with TBI. Further research is warranted to compare the components of inpatient rehabilitation.

Long-Term Impacts on Adult Psychopathology

Giannopoulou et al., (2018) looked at the long-term impacts of hypoxia on brain chemistry. The research design used to conduct the study was quantitative, using population-based cohort studies. The participants were identified for long-term study from prenatal through age 7 and then followed once aged 18-27, comprised of one cohort in the UK

and one cohort in Sweden. The study summarized epidemiological data on fetal hypoxia. Both obstetrical hypoxic events on the prenatal fetuses and post-natal events were identified and subjects were followed into childhood and early adolescence to evaluate the association or risk of later psychopathology. The results of the research study acknowledged the impacts of cognitive, social, and motor development. The impacts were attributed to the immunohistochemical effect of hypoxia and the role that could play in predisposing survivors to dopamine-related neurological or cognitive deficits. They found a direct correlation between perinatal hypoxia and a predisposition to cognitive impairments. The theoretical implication would provide an opportunity for histochemical testing to become a baseline for diagnosing potential cognitive, social, and motor development impact.

Treatments and Interventions

Physical Interventions

Tu et al., (2019) measured the efficacy of reoxygenation for therapeutic treatment of hypoxia. The research design used was quantitative, using animal experimentation for data collection. Twenty-four mice were in each model, and 3 models were performed during the study. This study was approved by the ethics committee of the Children's Hospital of Chongqing Medical University, Ministry of Education Key Laboratory of Child Development and Disorders, China. Previous attempts at reoxygenation during cardiopulmonary bypass procedures (CPB) resulted in the oversaturation of tissues causing cytotoxic hyperoxia. This study looked at the use of controlled reoxygenation beginning at the patient's preoperative saturation rate and increasing at a controlled rate. The data supports a finding of reduced apoptosis in neurons and glial cells, implying an overall reduction of injury. While this study was conducted on mice, it provides

insight and direction to treatment parameter considerations in human patients undergoing CPB procedures.

Dobson et al., (2017) measured the efficacy of treating hypoxia with 10 mg of caffeine. The research design was quantitative experiments for data collection. Dobson's study looked at twenty-seven infants born <32 weeks, diagnosed with intermittent hypoxia, and treated with 10mg caffeine. A control group of 53 infants were monitored. Findings were positive and reduced the impact of intermittent hypoxia by 36-38 weeks. The implication of this provides an opportunity for treatment at the onset of a hypoxic event.

Bruschettini et al., (2018) determined the efficacy and safety of stem cell-based interventions for the treatment of hypoxic-ischaemic encephalopathy (HIE) in newborn infants. The research design used will be quantitative experiment and data collection. Participants will be term infants (37 weeks or greater) and late preterm infants (34+0 to 36+6 weeks' gestation) 10 days of age or less, with evidence of peripartum asphyxia. This is ongoing research recognizing the need for new therapies at the onset of events. The implication of this is that research is beginning to recognize the value of early intervention.

Behavioral Interventions

Adigüzel et al., (2018) focused on rehabilitation comparison between anoxic brain injury and traumatic brain injury. The research design was a quantitative study observing a cohort of 40 patients. Participants were partnered ABI to TBI with equivalent Functional Independent Measurement score. The multiple linear regression analysis showed that intensive care unit length of stay had an inverse relationship with the Functional Ambulation Calculation score change. No significant differences were found between the ABI and the TBI scores. The

implication of this study is that many of the therapies beneficial to traumatic brain injury patients may also be of benefit to patients with anoxic or hypoxic injury.

De Nardi et al., (2020) explored the utilization of social media by adolescents with chronic illnesses, including catalysts, pros and cons, and desired outcomes. This was a qualitative study using a cross-sectional case study as its research design. The 212 participants were between the ages 13 and 24, diagnosed with any of 4 chronic illnesses, including IBS, celiac disease, diabetes, and/or cystic fibrosis. The results of the study showed that 97.6% of children self-reported a desire to share their experience with peers, and during an active disease phase social media time increased from an average of 5 to 11 hours to meet that need. 94.3 % of participants searched for new connections with peers within their diagnosis. The implications of this study shows the inherent need of children to develop social relationships with peers is strong enough that children will seek out creative means to meet that need, even if unconventional.

Benefits of Early Intervention

Formisano et al., (2016) evaluated data in order to understand the relationship between the time interval from being injured to rehabilitation. This was a quantitative study. This study used observation to help collect data. Data collection was acquired through 29 rehabilitation facilities with units for severe anoxic brain injury. The participants in this study consisted of 1,470 participants aged between 18 to 83 years all patients were documented by brain-computer tomography or MRI recorded within the first 2 hours of injury. They were divided into three groups: TBI, CVA, and anoxic brain damage. Participants were further divided into time intervals from injury to rehab admission. The results of this study were patients that were presented with the opportunity with admission to a rehabilitation facility early had less adverse

impact than those with delayed intervention. The implication of this study is the direct correlation between early intervention and positive outcomes including fewer long-term disabilities.

Barriers to Interventions

Albrecht et al., (2017) explored barriers to diagnosis and treatment for patients with traumatic brain injury. The research design of this study was qualitative, using focus groups and interviews. Thirty-three participants included 10 health care providers, 18 patients with traumatic brain injury, and 5 caregivers. The results of the study identified that barriers include poor physician education, insurance benefit hurdles, and economics. The implications were that more research should be focused on pilot interventions aimed at the identified barriers for earlier intervention.

Discussion

Review Analysis

In a comparison of the data available in the above articles, certain trends became apparent. Those trends were divided into three categories, impacts and long-term effects, new diagnostics and interventions, and benefits and barriers to interventions. None of the articles were in direct conflict with previous research. Articles either broadened understanding, discovered new variables to be considered regarding areas of physiological impact or treatment opportunities, and identified areas for future research.

Two of the studies were animal-based (Ehltling et al., 2022; Tu et al., 2019) the remaining eleven were human participants. Five of the articles measured and defined adverse impacts directly attributable to chronic hypoxia. Four of the five articles clearly identify chronic health as

having an adverse impact resulting in lower overall life satisfaction and higher psychosomatic health complaints (Berkelbach et al., 2021; Brady et al., 2020; Harbinson et al., 2017; Giannopoulou et al., 2018). Three of the five articles identify social development and peer relation problems in direct correlation with chronic illness (Berkelbach et al., 2021; Bardy et al., 2020; Giannopoulou et al., 2018). The data collection methodology in all of the above articles was questionnaires or interviews where participants self-reported. The combined data pool of 20,292 participants is sufficient to support that self-reported adverse impacts due to their chronic illness is sufficient evidence to support the finding that chronic illness results in adverse impacts across multiple developmental stages including cognitive, physical, and social.

Five of the studies focused on research regarding interventions. Four studies looked at physical interventions. Two focused on the direct treatment of hypoxia (Bruschettini et al., 2018; Tu et al., 2019; Dobson et al., 2017), and one focused on physical rehabilitation (Adigüzel et al., 2018). The final three articles focused on the benefits and barriers to interventions (Albrecht et al., 2017; Formisano et al., 2016).

Considerations

According to The Department of Health and Human Services (2023), the Affordable Care Act has provided great strides in access to services and linking physical medicine and mental/behavioral health therapies to provide care for the complete person. Berkelbach van der Sprenkel et al. (2021) reports that in the United States, the percentage of children growing up with chronic diseases increased from 12.8% in 1994 to 26.2% in 2006. This clearly represents the need for a better understanding of the adverse impacts that chronic medical challenges have on psychosocial development in children living with physical illness. Understanding how one aspect impacts the other is beneficial not only to the patient and their well-being, but to

physicians, educators, parents, and advocates to be able to initiate appropriate support when needed through all stages of potential impact.

This paper focuses on recent research expanding the area of study on chronic hypoxia, specifically how it adversely impacts developmental stages. All of the reviewed research flows from causation, physiological impact, and functional impact, to interventions and benefits of early intervention. This paper will examine the direction of how chronic physiological and functional impairments, in turn impact mental and behavioral health, cognitive capacity, executive function, short-term memory, and interpersonal relationship development-both with peers and in another social setting such as the classroom. The evidence will show that without interventions these adverse impacts can be long-term into adulthood. David Barker proposed the Fetal Onset of Adult Disease (FOAD) hypothesis in the late 1980s. Simply put he felt that all adult diseases could be traced back to adverse impacts during fetal development (Wang et al., 2020). This is compounded when the issue is chronic (Ehltling et al., 2022).

First, understanding the etiologies and presentation of chronic hypoxia is valuable for this paper in that it demonstrates multiple disciplines could be engaged with the patient in determining diagnosis, treatment strategies, and long-term outcomes. Nalivaeva et al., (2018) concluded that prenatal hypoxia diminishes brain adaptive potential and plasticity, especially in the cortex and hippocampus. Additionally, prenatal hypoxia has a significant impact on normal brain function and epigenetic regulation. Authors call for further studies to better understand the changes that happen on a molecular and epigenetic level that shape one's development in postnatal life. Piešová et al., (2020) compiled a literature review of 80 papers spanning from 2000-2018 to summarize the current literature on the impact of perinatal hypoxia. The research was divided into peri and post-natal hypoxic events identified as either environmental or

placental origins. The subjects of research consisted of both human and animal, both live and post-mortum. They measure postnatal growth and sensorimotor development, motor functions, activity, emotionally, learning ability, and impacts specifically on the hippocampus and corpus striatum. Their work concluded that there were delays measurable in all categories of motor, emotional/social, and cognitive and can span into adulthood. The implication of this study is that hypoxic damage can be long-term beyond the capacity of neuroplasticity to self-resolve.

This was followed by a literature review compiled by Di Fiore et al., (2021) regarding the differences from acute severe injury, a chronic progressive disease state, and intermittent hypoxemia. They studied both animal and human populations and used both naturally occurring hypoxic events and induced hypoxic events. They concluded that intermittent hypoxia could be successfully treated if intervention is early and the underlying cause remains in remission. These reviews laid a foundation for the research by Ehltling et al., (2022), documenting data regarding the timing and impact hypoxic ischemia can have in a rat model. They found that over time the damage increased to, on average, over 50% in a smaller brain. The implication of this study was that chronic hypoxia produces an accumulative impact over time.

Next, this paper looks at impacts specifically on developmental stages. Bass et al., (2004) concluded that there is evidence of adverse impacts from chronic or intermittent hypoxia on development, behavior, and academic achievement. Harbinson et al., (2017) compared functional and psychosocial outcomes in patients with hypoxic-ischemic brain injury to people who have had a traumatic brain injury. Study results suggest that patients with HIBI achieve fewer long-term functional improvements compared to patients with TBI.

Then Giannopoulou et al., (2018) narrowed their scope of study to look at how hypoxia impacts brain chemistry. The study summarized epidemiological data on fetal hypoxia. Both

obstetrical hypoxic events on prenatal fetuses and post-natal events were identified and subjects were followed into childhood and early adolescence to evaluate the association or risk of later psychopathology (Giannopoulou et al., 2018). They acknowledge the impacts reviewed above, cognitive, social, and motor, but strive to determine the immunohistochemical effect of hypoxia and the role that could play in predisposing survivors to dopamine-related neurological or cognitive deficits. They found a direct correlation between perinatal hypoxia and a predisposition to cognitive impairments. Piešová et al., (2020) outlines the pathways identified for hypoxic-induced brain injury. They document how hypoxia leads to excitatory amino acids, inflammation, and gene expression changes, which then lead to mitochondrial dysfunction, reactive nitrogen, protein, and lipid oxidation resulting in cellular damage, necrosis, or apoptosis.

Piešová et al., (2020) work concludes that there were delays measurable in all categories of motor, emotional/social, and cognitive and can span into adulthood. They hope their current findings help support the foundation of new anti-hypoxic therapy. Their article not only supports the findings from Giannopoulou et al., (2018), it builds on them. It follows subjects and shows that the impact is long-term. Any superficial inconsistencies result from the fact that as new questions are asked, the expanding foundation for understanding evolves. Yet, overall, this evolution supports past research in that hypoxia has a definite impact on cognitive function and brain chemistry. This is further supported by Brady et al., (2020), suggesting chronic illness adversely impacts, social development in early adolescence and, whether physical or cognitive in nature, leads to increased rates of mental illness. The authors found that the illness directly and/or the mental health impact resulted in higher rates of school absenteeism. Self-reporting surveys were collected and assessed, expanding on this finding. The average z-scores were calculated showing significant disparity in life satisfaction, psychosomatic health complaints,

conduct problems, and peer problems than their healthy peers Berkalbach et al., (2021). This supports that Barker's hypothesis bears consideration when looking at the correlation between adult pathologies to a fetal origin. There are strong links between FOAD, specifically in perinatal hypoxia/chronic hypoxia, as one of the most common complications to alter brain function and structure, resulting in a spectrum of neurological deficits and disorders (Wang et al., 2020).

The link between hypoxia and cognitive impact has been well documented. Historically it has been associated with known events such as premature births with underdeveloped lungs, congenital heart defects with mechanical insufficiency for oxygen transport, cerebral vascular accident or traumatic brain injury with barriers prohibiting oxygen saturation of neural tissue, or any state that promotes a condition where there is low arterial oxygen supply that inhibits either oxygen transport or oxygen saturation of tissues (Piešová et al., 2020). Di Fiore et al., (2021), differentiates between acute severe injury, a chronic progressive disease state, and intermittent hypoxemia. Both animal and human populations were studied using both naturally occurring hypoxic events and induced hypoxic events. They concluded that intermittent hypoxia could be successfully treated if intervention is early and the underlying cause remains in remission (Di Fiore et al., 2021). Direct interventions include reoxygenation or pharmacological interventions such as caffeine citrate (Tu et al., 2019; Dobson et al., 2017). Tu et al., (2019) demonstrates how apoptosis is reduced in neural and glial cells through controlled reoxygenation, implying an overall reduction of injury. Previous attempts at reoxygenation during cardiopulmonary bypass procedures (CPB) resulted in the oversaturation of tissues causing cytotoxic hyperoxia. While this study was conducted on mice, it provides insight and direction to treatment parameter considerations in human patients undergoing CPB procedures. This supports Di Fiore's recommendation for reoxygenation as a potential intervention. Dobson et al., (2017) shows a

successful use of caffeine as a physical intervention to reduce the adverse impacts of hypoxia. Other pharmacological interventions such as neuroserpin, provide neuroprotective factors with favorable outcomes for hypoxic post-ischaemic injury (Millar et al., 2017). Current ongoing stem cell research also looks promising as a potent intervention for fetal onset hypoxia (Bruschettini et al., 2018). These studies show that intervention reduces the hypoxic impact on brain function. The importance of these research projects is that they show encouraging results in reducing hypoxic impact with early intervention, contrary to previous policies of relying on neural plasticity to mitigate the impact.

As noted above, chronic hypoxia has an accumulative adverse impact (Ehltling et al., 2022). Even with early interventions, i.e., surgical, pharmacological, or reoxygenation, when mitigation is not complete, hypoxia continues to impact brain chemistry, structure, and function. This, in turn, results in cognitive, motor, and psychosocial development deficits that can still benefit from early assessment and intervention (Brady et al., 2020; Piešová et al., 2020; Giannopoulou et al., 2018; Di Fiore et al., 2021). Many of the rehabilitations for traumatic brain injury were beneficial to patients with anoxic or hypoxic injuries. They include functional ambulation, speech therapy for memory, executive function, and spatial awareness, physical therapy for fine and gross motor skills acquisition, and psychological therapy for depression, ADHD, anxiety, and OCD (Giannopoulou et al., 2018; DiFiore et al., 2021). Academic accommodations help to maintain peer interaction and relationship development by supporting students to remain in their peer groups by offsetting or mitigating cognitive delays (Bass et al., 2004; Berkelbach et al., 2021; Giannopoulou et al., 2018). These peer groups are of vital importance during childhood and adolescents for patients with chronic conditions. Students self-reported not wanting to be identified as different or “other” and choosing isolation as

opposed to engagement in order to shield themselves from judgment, ridicule, or victimization, whether real or imagined. Brady et al., (2020) speculated that the burgeoning self-awareness during adolescence builds the desire to want to appear “normal” in the eyes of their peers. This drive was strong enough that 97.6% of children self-reported a desire to share their experience with peers, and during an active disease phase, social media time increased from an average of 5 to 11 hours to meet that need. 94.3 % of participants searched for new connections with peers within their diagnosis (De Nardi et al., 2020).

Overwhelming consensus from the literature reviewed agrees that the benefits of early intervention are measurable whether direct physical interventions (Tu et al., 2019; Dobson et al., 2017; Bruschetti et al., 2018) or rehabilitative interventions sustained throughout intermittent or chronic phases (Brady et al., 2020; Berkelbach et al., 2021; Harbison et al., 2017; Giannopoulou et al., 2018; Adigüzel et al., 2018; Cope et al., 1982; Formisano et al., 2016). Groswasser et al., (1989) first documented in a study group of 31 patients with anoxic brain injury, that those who were referred in 24 hours for rehabilitation had a relatively better outcome than those with delayed referrals. Groswasser confirmed the findings of Cope et al., (1982). Cope et al., measured the benefit of early intervention in patients with head injuries of various causes through a study where participants were divided into two groups matching for age, level of disability, and other factors to rule out bias. Findings indicated that patients with delayed treatment required twice as much acute rehabilitation than patients with early intervention. These findings were supported through a study by Formisano et al., consisting of 1,470 participants divided into three groups based on diagnosis, and further into two groups based on the time interval from diagnosis to rehab admission. Patients that were presented with the opportunity

with admission to a rehabilitation facility early had less adverse impact than those with a delayed intervention (Formisano et al., 2016).

While everyone is in agreement that early intervention is key to improving long-term outcomes and overall quality of life, it's important to recognize that there are barriers that separate patients from receiving these life-altering services and accommodations. Albrecht et al., (2017) cites these barriers include poor physician education, insurance benefit hurdles, and economics. These findings build on the research of Maddox et al., (2016), which identifies additional barriers that may include a lack of home support system, transportation to and from appointments, insurance or lack of insurance, timeliness of referrals, disparities may also be due to ethnicity, economic, race, and age. Authors felt strongly that more than the medical community needs to work to remove these barriers, including policymakers, insurance, and researchers. Knowing and identifying the barriers to rehabilitation helps formulate solutions and provides a platform for a measurable difference in outcomes. Research has identified other professional disciplines that may be able to identify the need for rehabilitative interventions, primarily consisting of educators and social workers (Brady et al., 2020).

Implications

The contributions included in this literature review confirm or broaden the understanding of the adverse impacts of chronic hypoxia. The literature was diverse in that it covered a broad spectrum of causes, diagnostic tools, treatments, expected outcomes, benefits of early intervention, and barriers to access. In reviewing the literature, several trends rose to the surface. These trends include:

- Dopamine deficits predispose to developmental delays, implication is that measuring histochemicals could identify risk factors (Giannopoulou et al., 2018).

- New control measures reduce over-saturation and potential for cytotoxic hyperoxia making reoxygenation during cardiopulmonary bypass procedures safer and more effective (Tu et al., 2019).
- Intermittent hypoxic events and chronic hypoxia produce adverse impacts that are accumulative and progressively alters brain chemistry, structure, and function (Di Fiore et al., 2021; Ehlting et al., 2022).
- When pharmacological interventions are appropriate, therapies such as caffeine or neuroserpin can offer neuroprotection, reducing oxidative stress (Dobson et al., 2017; Millar et al., 2017).
- Brain plasticity may not be sufficient to overcome hypoxic injury (Nalivaeva et al., 2018; Piešová et al., 2020).
- Untreated neonates by age of 2-5 years are 50-60% reported as developmentally normal. 18% of patients were identified as having severe sensorimotor learning disabilities (Millar et al., 2017).
- Hypoxia-induced brain injury achieves less long-term functional improvements compared to patients with traumatic brain injury. Also noted was an increase in psychosocial impact long term (Harbinson et al., 2017).
- Increased compromise to brain chemistry, structure, and function result in chronic physiological and functional impairments, in turn impact mental and behavioral health, cognitive capacity, executive function, short-term memory, and interpersonal relationship development-both with peers and in another social setting such as the classroom (Brady et al., 2020; Berkelbach et al., 2021).

- Early intervention improves long-term outcomes (Bruschettini et al., 2018; Cope et al., 1982 Formisano et al., 2016; Adigüzel et al., 2018; De Nardi et al., 2020).
- School absenteeism or peer victimization is flagged as a key factor for identifying students with underlying medical conditions that need medical assessment and referral for possible intervention or accommodation (Brady et al., 2020).

The literature reviewed was diverse in what aspects of hypoxia they examined, from topics of causes, diagnosis, treatments, rehabilitation, and long-term outcomes. The trends above lay a foundation for therapeutic improvements, opportunities for intervention, and future research.

Limitations and Future Directions

Each of the studies in the literature reviewed could have benefited from larger sample sizes in their studies. It is possible that the subject matter did not lend itself to having a larger population to study. Considering the new era of HIPAA and electronic medical records that lends itself well to utilizing anonymous data records, it would be of interest for future research to see if a more robust sample size supports the findings. That would require chart notes to include some of these early detection methodologies to have any substantial value as data. Future research would hopefully continue to expand options for early detection and treatment options.

Almost all of the studies used had certain limitations. Dobson et al., (2017) states that they were only able to have a record of the 38 weeks instead of the 40 weeks that they wanted. Another limitation this study suffered from was not having enough infants enrolled in the study; they felt that if they had more infants for their study, then it would help the interpretation of their results from the study. Tu et al. (2019) did not differentiate the glial cells from neurons in the study, and they didn't differentiate females and males, they hope that is something that can be

fixed with future research. Future research should include an examination of the effect in all levels of desaturation. The implication of this study is that hypoxia should be considered for intervention when examining the development, behavioral, or academic delays.

Berkelbach van der Sprenkel et al., (2021) shows that chronic illness has doubled from 1994 to 2006. It would be interesting to see what the current data shows. This would be interesting to look at the correlation between chronic illnesses/emotional deficits and suicide rates. Also, we saw that adverse impacts are not just directly attributed to chronic childhood illness but can also be attributed to any close family member with a chronic illness. Epigenetics has looked at generational impacts in other fields, and future research could focus on looking at what is the impact of chronic illness on families generationally. None of the studies considered other variables that may affect psychosocial functioning among adolescents with a chronic disease—such as school functioning, resilience, and sleep. Understanding the implications of how these variables could contribute to or inhibit psychosocial development may be beneficial.

More work needs to be done to reduce barriers to access (Maddox et al., 2016; Albrecht et al., 2017).

Conclusion

I have a twofold investment in this research question. First, my career choice as a Child Life Specialist will put me in direct contact with children facing medical challenges that may benefit from both early detection and early intervention for hypoxic impact. Secondly, while my personal experience is anecdotal, it also supports the findings of the literature:

1. Known hypoxic event. Born “blue” with congenital heart defects requiring immediate cardiopulmonary bypass surgical intervention with oxygen saturation at 64%.

2. Nine additional major surgical interventions over fourteen years requiring multiple cardiopulmonary bypass (CPB) experiences.
3. Chronic hypoxia from bidirectional Glenn procedure that maintained oxygen saturation between 75 and 85%.
4. Developmental delays throughout infancy, childhood, and adolescence with no referrals for intervention or evaluation on the impact of deficits on cognitive, motor, and social development. Parents and educators thought that my “ditzzy blonde“ was just my normal state of being. By junior high, I was so far behind academically that I was failing most every course. Physically I was unable to barely walk across the room without becoming short of breath.
5. In my freshman year of high school, I experienced a cardiovascular accident during surgery resulting in a right hemispheric brain injury and complete left-side deficits. Received my first referral for neuro-psych evaluation and IEP/504 in 2015, which then was the catalyst for me to receive occupational, physical, and speech therapy along with academic support.

This opened the door for a completely different experience in both academia and life in general.

When I first came across some of these articles, I was working on a paper for a psychology class, and it helped shed light on why I had faced many challenges academically, physically, and socially. I had to wonder, what if I had been referred and evaluated, and provided support earlier? How would it have impacted my life both socially and academically?

In conclusion, the literature reviewed in this project clearly supports that hypoxia can adversely impact childhood developmental stages, and its consequences can be long-term, reaching into adolescence and even adulthood. Hypoxic events, be they acute, intermittent, or

chronic, can impact any stage of fetal or infant development, including growth hormone production, proteins development, mitochondrial function, organ development, and brain chemistry homeostasis, resulting in developmental delays in fine and gross motor skill acquisition, cognitive capacity, and psychological pathologies. According to the literature, these hypoxic events can be direct—primary, as in congenital defect disrupting mechanical transport of oxygen, direct - secondary, as in surgical complication when CPB is used, or indirect, as when either the mother has a hypoxic event that is relayed to the fetus, or there is a placental insufficiency that inhibits oxygen transfer during fetal development.

The literature suggests by implication of its findings that early detection is beneficial, as is early intervention. Research has provided opportunities across disciplines to identify patients that would benefit from assessment referrals and interventions or accommodations. After reviewing the literature, it is my opinion that early detection and intervention should become the norm to reduce or hopefully fully mitigate cognitive, psychological, and social deficits of chronic hypoxia in early childhood and adolescent development. Because chronic hypoxia diminishes brain adaptive potential and plasticity, early intervention is paramount to the best possible outcomes.. The Affordable Care Act has provided the opportunity where all professionals can have the potential of choreographing patient care across disciplines. While great strides are taken to mitigate acute hypoxia impact, more effort is needed across multiple disciplines to provide access, assessment, and rehabilitation to reduce adverse impacts and improve long-term outcomes for those suffering from chronic hypoxia.

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