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Cognitive development in Ecuadorian children with PKU

.

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RESUMEN

En este estudio se examina la asociación entre la fenilcetonuria (PKU) y los déficits cognitivos en niños ecuatorianos. La PKU es un trastorno metabólico provocado por variaciones en el gen PAH. La principal anomalía bioquímica de la PKU, la hiperfenilalaninemia, provoca problemas en la síntesis de proteínas y neurotransmisores cerebrales. Los trastornos relacionados con la disminución del desarrollo cognitivo pueden prevenirse con gran éxito siguiendo una dieta estricta baja en fenilalanina.

La identificación tardía de la fenilcetonuria, una enfermedad degenerativa, puede causar problemas de neurodesarrollo. Sin embargo, no está claro qué partes del cerebro se ven más afectadas. Dada la ausencia de cribado postnatal en Ecuador, la PKU se descubre con frecuencia muchos años después del nacimiento. El objetivo de este estudio es examinar el estado cognitivo de los niños ecuatorianos afectados por la PKU. Se evaluarán los niveles de inteligencia y función ejecutiva de 20 niños (de 3 a 16 años) de la región de Quito y Salcedo en mayo de 2023 utilizando el WPPSI-IV, el WISC-V y el NEPSY-II (los resultados preliminares estarán disponibles en junio). Por lo tanto, este estudio tiene la capacidad de ofrecer más información sobre los posibles déficits relacionados con la PKU y allanar el camino para futuras investigaciones que permitan crear programas terapéuticos y psicoeducativos.

Palabras Clave: PKU, Funciones Ejecutivas, PAH

ABSTRACT

In this study, the association involving phenylketonuria (PKU) and cognitive deficits in Ecuadorian children is examined. PKU is a metabolic disorder that is brought on by variations in the PAH gene. The primary biochemical aberration in PKU, hyperphenylalaninemia, causes problems with the production of brain proteins and neurotransmitters. The disorders related to decreased cognitive development can be prevented with great success by following a strict low-Phenylalanine diet.

Late identification of PKU, a degenerative condition, can cause neurodevelopmental problems. It is unclear, though, where parts of the brain are most impacted. Given the absence of postnatal screening in Ecuador, PKU is frequently discovered many years after birth. The purpose of the subsequent study is to look at the cognitive status of PKU-affected kids in Ecuador. 20 children (ages 3 to 16) from the Quito and Salcedo region will have their intelligence and executive function levels evaluated in May 2023 using the WPPSI-IV, WISC-V, and NEPSY-II (preliminary results will be available in June). This study therefore has the ability to offer more information on potential PKU-related deficits and pave the way for future research to create therapy and psychoeducational programs.

Key Words: PKU, Executive Functions, Cognitive Impairments,

TABLE OF CONTENT

ABBREVIATIONS

PKU: Phenylketonuria

PAH: Phenylalanine hydroxylase

HPA: Hyperphenylalaninemia

BH4: tetrahydrobiopterin enzyme

WPPSI: Wechsler Preschool and Primary Scale of Intelligence

WISC: Wechsler Intelligence Scale for Children

Phe: Phenylalanine

LNAA: Large neutral amino acids

ADHD: Attention-deficit/hyperactivity disorder

NBS: Newborn screening

Introduction

Phenylketonuria (PKU) is an uncommon hereditary condition which affects about 6.002 per 100,000 newborns worldwide (Shoraka et al., 2020). It is a recessive disorder and an inborn metabolic condition caused by pathogenic mutations in the phenylalanine hydroxylase (PAH) gene; most frequently resulting in a non functional PAH gene. In some cases there is an incidence of hyperphenylalaninemia (HPA) which is a condition where increased quantities of phenylalanine in the body affect the brain by altering the classic/normal pathways of myelination, protein and neurotransmitter synthesis (Surtees & Blau, 2000) (van Spronsen et al., 2021).

Untreated PKU can cause intellectual disabilities, seizures, microcephaly, and growth failure due to the accumulation of hazardous by-products of phenylalanine (Williams et al., 2008). Newborn screening allows for early diagnosis of the disease. Research shows that early dietary intervention, consisting of a low-protein diet and phenylalanine restriction, can successfully halt the progression of metabolic and pathological consequences, including intellectual impairment (Williams et al., 2008). Even though there is prevalence of PKU in Ecuador, there is a lack of research in Latin America. Therefore, this research will focus on Ecuador's PKU children population, in a country where awareness and research in regards to this disorder is almost non-existent. This study will implement two Weschler's tests on Ecuadorian children from 2 to 17 years old, to identify the relationship between PKU and cognitive impairment. The Wechsler Preschool and Primary Scale of Intelligence IV (WPPSI-IV) and the Wechsler Intelligence Scale for Children (WISC-V) will be applied in this study. Future studies could develop treatment and psychoeducation programs, as well as potentially provide more insight to the possible impairments related to PKU.

Theoretical Background

Biology of PKU

Phenylketonuria (PKU) is an autosomal recessive metabolic disorder, where heterozygous carriers will not experience any of the signs and symptoms of the disease. It is necessary for both alleles to have the mutation in the PAH gene for PKU to develop (Summaily & Mujamammi, 2017), which manifests as high blood levels of phenylalanine (Phe) The enzymes in the PAH gene that transform Phe to tyrosine (Tyr), or the cofactor for that enzyme, tetrahydrobiopterin (BH4), can both be deficient or entirely lacking (van Spronsen et al., 2021). According to its intended use, BH4 contributes to the production of neurotransmitters as well as the catalytic behavior of PAH in the transformation of Phe to Tyr (Summaily & Mujamammi, 2017). Phenylalanine competes with other crucial amino acids like tyrosine and tryptophan for passage through the blood-brain barrier (Ashe et al., 2019). Amino acids play an important role in the synthesis of neurotransmitters. "The biosynthesis of the neurotransmitter monoamines dopamine,noradrenaline and serotonin is dependent upon the availability of the precursor amino acids tyrosine and tryptophan within the brain and the presence of a normal Phe concentration" (Surtees & Blau, 2000). Because of this, there may be issues with mood and behavior when the concentration of crucial neurotransmitters like dopamine and serotonin decreases (Ashe et al., 2019).

This metabolic pathway is essential for the breakdown of roughly 90% of the daily dietary intake of Phe. PAH deficiency causes Phe to build up in blood. Hyperphenylalaninemia (HPA), a condition where blood Phe concentrations are exceeded, is the core biochemical abnormality in PKU disorder (van Spronsen et al., 2021). PKU can cause phenotypic changes such as intellectual impairment, behavioral and mental problems, seizures, and mobility disorders (Ashe et al., 2019).

Diagnosis and Prevalence

Studies demonstrate that the incidence of PKU varies worldwide. Due to the nature of autosomal recessive inheritance of PKU, conjoint marriage is a significant risk factor (Shoraka et al., 2020). Among the countries with the highest prevalence is Iran, with a ratio of 1:4,698 (Shoraka et al., 2020). Nevertheless, no study has thoroughly evaluated the prevalence of PKU among areas, nations, or sources of heterogeneity. To identify affected individuals early on and treat them with a specialized diet to prevent cognitive development difficulties, postnatal screening for PKU is crucial. The screening consists of pricking the heel of a healthy newborn to get a drop of blood, which is sent for testing. Neonatal screening is typically done before the newborn is let go from the hospital. However, if a baby is not born in a hospital, it is the responsibility of the parents to make arrangements for a quick medical examination to spot and treat any potential illnesses.

Mitigation strategies

When there is an early diagnosis, treatment commences soon after birth. The fundamental basis of treating PKU is a reduced Phe diet which is sometimes complemented with L-amino acids and are Phe-free (van Wegberg et al., 2017). Therefore, beef, fish, eggs, poultry, bread, and pasta are mainly avoided in the diet because of their high Phe content (Ashe et al., 2019). Nevertheless, there is a chance of possible nutritional deficiencies when using this method. According to studies done by Summaily & Mujamammi (2017), a Phe-restricted diet may cause growth retardation or an early-onset osteoporosis if certain vitamins or minerals aren't consumed in suitable amounts. In addition to these hazards, following such a diet has enormous social and financial costs (Summaily & Mujamammi, 2017). Thereby suggesting that this rigorous treatment could negatively impact the patient’s social life and their personal economic standards.

Supplements

Some patients are given nutritional supplements to compensate for those important vitamins and nutrients from the food they are unable to intake. Alternative dietary supplements like glycomacropeptide or large neutral amino acids (LNAA) may be used in PKU treatment facilities (van Wegberg et al., 2017). For some individuals who respond to this therapy, BH4 may be administered as sapropterin dihydrochloride, acting as a pharmacological facilitator (van Wegberg et al., 2017). It has been proven that a stringent low-Phe diet works well to prevent PKU-related cognitive impairment and should be followed long-term to lessen the neurodevelopmental effects on the patient's adult brain (Widaman, 2009, as cited in Stone et al., 2023). Phenylalanine dietary restriction has been the main route of treatment for more than 60 years and has been found to be quite successful. However, there is further research to be made on dietary supplementation since there is a lack of investigation in testing it on children under 11 years old. Some investigations show that LNAA supplementation is often only considered for elderly individuals who have trouble following dietary limitations (Rocha & MacDonald, 2016).

New research is considering treating PKU using enzyme treatment. Regardless of the illness genotype, this approach entails altering the PAH metabolism phenotype, which can aid in reducing the dangerous accumulation of Phe in the bloodstream (Summaily & Mujamammi, 2017). Enzyme substitution using PAL or PAH are the two methods of enzyme treatment that are available. Studies on mice have demonstrated that fusion proteins can effectively replace PAH (Summaily & Mujamammi, 2017). Nevertheless, an immunological reaction to the enzyme is one potential risk of enzyme therapy for PKU, which may lessen its efficacy or result in negative side effects in the patient. Additionally, there is few long-term safety data available, and there might be additional unidentified risks related to this kind of therapy. In

addition, gene therapy is something that has been considered as a treatment in PKU, however, it has not gone past the trials of mouse models.

PKU and the brain

By lowering other LNAAs, such as tryptophan and tyrosine, which are required for the formation of serotonin and dopamine, HPA arising from PKU interferes with the synthesis of cerebral proteins and neurotransmitters (van Spronsen et al., 2021). This suggests that the ability of the brain to produce proteins and neurotransmitters may be compromised. Phe has also been demonstrated to inhibit the transmission of glutamate, a crucial neurotransmitter involved in memory, learning, and synaptic plasticity (Ashe et al., 2019). Reduced neocortical synaptic density, aberrant myelination, and defective dendritic trees can all be consequences of this disruption (Ashe et al., 2019). "Glutamate is the most abundant neurotransmitter and plays an important role in synaptic plasticity, learning, memory, and modulation of function within the limbic system" (Ashe et al., 2019). Glutamate is also involved in stress-related illnesses like anxiety and depression (Ashe et al., 2019). In contrast to acute stress, which can boost glutamate production and transmission, chronic stress is linked to findings that are comparable to those of hyperphenylalaninemia. Reduced synaptic plasticity and diminished glutamatergic neurotransmission are seen in both long-term stress and hyperPhe, which may aid in the emergence of anxiety and depression (Ashe et al., 2019).

Psychiatric disorders

Since dietary restriction has become a viable way to treat the correlation between PKU and cerebral damage, other diagnoses such as attentional, behavioral, and mood disorders tend to go unrecognized (Targum & Lang, 2010). Various investigations have demonstrated how PKU affects metabolism, cognitive abilities and dietary lifestyle. However, there also are psychological and psychosocial factors that impact diagnosed people and their families. Even

early treated children tend to exhibit struggles with attention, learning outcomes, motivation, interpersonal abilities, independence, and self-esteem (Brumm et al., 2010). As patients enter into adulthood there is still a prevalence of social deficits such as low self-esteem and lack of autonomy which could potentially lead to anxiety disorders, phobias, decreased positive feelings, and depressed mood (Brumm et al., 2010). Additionally, living with a chronic illness has an enormous psychological impact on individuals. The burden of maintaining rigorous dietary treatment and follow-up may function as a psychological stressor for both those with the disease and their family (Manti et al., 2016). Patients who struggled to follow the nutritional recommendations during their first ten years of life had a higher chance of receiving a diagnosis with a psychiatric condition (Manti et al., 2016).

As previously mentioned, HPA has a variety of effects on brain function, including disruption of amino acid transport across the blood-brain barrier, anomalies in myelin, and decreases in neurotransmitters. These factors all probably play a role in the development of neuropsychiatric symptoms. Depression has a higher rate of prevalence in adults with PKU, and there are likely different causes to it. The adherence to the PKU treatment diet may interfere with the neurochemical biological process and is thought to have an impact on complex mental diseases like depression (Ashe et al., 2019). Given the significant rise in the prevalence of depression in PKU and the essential functions that dopamine, norepinephrine, and serotonin serve in controlling thought, emotion, and mood, depressive symptoms are probably strongly linked to the reduced central monoaminergic transmission that HPA causes (Ashe et al., 2019). A deficit in these monoaminergic networks is associated with depression, since frontal cortical regions play a critical role in mood modulation (Ashe et al., 2019).

In comparison to the general population (9.2%), the incidence of anxiety disorders is significantly greater (15.6%) in the adult PKU population (Bilder et al., 2017). Low

norepinephrine and serotonin in the brain is related to various anxiety disorders such as generalized anxiety, panic disorder, specific phobias, obsessive-compulsive disorder and more (Ressler & Nemeroff, 2000). Due to the nature of the disease, the high Phe levels in the blood play a huge role in low serotonin levels, creating an environment for the incidence of anxiety. In addition, children who did not get treatment continued to show externalizing symptoms like aggressiveness and agitation as well as mental impairment, in contrast to early-treated children, who showed symptoms related to self-isolation, phobias, and low self-esteem (Smith & Knowles, 2000).

In addition, some research in Brazil demonstrates that PKU is a serious risk factor for developing ADHD even after receiving regular therapy from birth. According to the research, a potential link between the two illnesses is through dopamine metabolism (Beckhauser et al., 2020). According to the Swanson, Nolan, and Pelham Questionnaire, 13 patients (38%) out of the 34 PKU-diagnosed people with an average age of twelve years old met the criteria for an ADHD diagnosis, with two having an inattentive type, six having a hyperactive or impulsive type, and one having an oppositional defiant disorder type (Beckhauser et al., 2020). The research shows how even early intervention has a toll on patients with PKU and their cognitive abilities. The discussion on the research attributes "a pathophysiological interface that involves the dopamine metabolic pathway may exist between the two conditions" (Beckhauser et al., 2020). As it has been presented, behavioral problems are also of high incidence in diagnosed patients with PKU. "Childhood Phe levels and internalizing problems for adult PKU patients were related; concurrent Phe was associated with both internalizing and externalizing behavioral problems for those under the age of 18" (Jahja et al., 2013). Therefore, according to data the underlying reasons of psychiatric disorders in PKU are complex, multidimensional, and comprise both physiological and psychological elements. For example, increased phenylalanine levels in the brain may have an impact on the

neurotransmitters serotonin, norepinephrine, and dopamine, which are crucial for controlling mood and behavior. A stringent low-phenylalanine diet may also cause stress and social isolation for those with PKU, which can contribute to the development of anxiety and depression.

Cognitive functioning in children with PKU

This research focuses on children with PKU. Therefore, there will be a review on the existing research on the cognitive function in early treatment and outcomes of late treatment in executive functions. During DeRoche and Welsh's (2008) investigation of a 25-year meta-analysis of 33 studies from 1980 to 2004 to examine the neurocognitive outcomes in PKU-affected children and adolescents they describe how treatment on nutritional diets are essential for cognitive performance. The study concludes by mentioning that PKU diagnosed children who receive early and continuous therapy will have IQ scores in the range of averages, but maybe lower than peers who are genetically related (DeRoche & Welsh, 2008). However, these individuals may struggle greatly with executive functioning, exhibiting rigidity of thought, inhibition, working memory, and planning (DeRoche & Welsh, 2008). Other studies reinforce this conclusion by mentioning that white matter deterioration is considered to play a key role in the PKU-related brain injury, especially in patients who get either no treatment at all or insufficient treatment (Ferreira et al., 2021). When left untreated PKU can cause seizures, eczema, autism, microcephaly, motor impairments, aberrant behavior, psychiatric disorders, and permanent intellectual disability if left untreated (van Wegberg et al., 2017). Brumm and Grant (2010) conducted a review of the literature and looked at the correlation between treatment characteristics, such as the start and length of therapy and blood Phe levels, and intellectual outcome from infancy to adulthood. While severe neurological and cognitive deficits caused by PKU have been successfully avoided by

current treatment methods, there may yet be space for improvement in terms of optimizing cognitive performance. The current definition of "controlled PKU" relies on keeping blood phenylalanine levels within normal ranges, although even then, cognitive performance might not be at its peak. In other words, blood Phe levels alone might not be the only thing affecting cognitive performance in PKU patients.

Executive functions

Executive functions are a collection of mental processes required for goal-directed behavior. Even in the presence of conflicting or irrelevant information, these systems serve as the brain commander in chief and are in charge of organizing and completing activities. Some cognitive processes referred to as executive functions include managing attention, preventing improper behavior, organizing information in working memory, and exercising cognitive flexibility. Advanced executive functions, such as planning, reasoning, and problem-solving call upon the simultaneous use of many fundamental executive functions (Welsh, 2002). “Reviews of executive functions have found that the most consistent phenylalanine-related impairments have been observed in working memory, sustained attention, and inhibitory control” (Jahja et al., 2013, as cited in Ashe et al., 2019). This suggests that there are different aspects of executive functions that are affected by PKU. However, the most common are related to memory, attention, and control.

Ecuador and PKU

All the research presented until now has been conducted in different countries around the world. However, there are a few studies demonstrating the prevalence and some factors about PKU in Ecuador. A program called newborn screening (NBS) aids in finding problems in babies that might impede their normal development or result in an early death. The program's objective is to identify congenital abnormalities early and provide therapy to stop

life-threatening consequences, intellectual and physical disability, and both. Blood samples are taken up to 8 days after delivery from babies at MPH health facilities as part of Ecuador's unified NBS program. The samples are submitted to an MPH facility in Quito for analysis.

Since 2011, the Ecuadorian Ministry of Health has been conducting a centralized newborn screening program to check for congenital hypothyroidism, phenylketonuria, galactosemia, and congenital adrenal hyperplasia (Pozo et al., 2021). A recent study evaluated the regional distribution of newborn screening cases in Ecuador. Spatial analytical tools were utilized to evaluate datasets from the national newborn screening program from January 2012 to December 2019 to establish the morbidity rates per 100,000 by disease and birth province. 2.2 million infants were born between 2012 and 2019, of whom 1.7 million were tested and entered into the database of the newborn screening program, which found 393 cases (0.02%) of congenital abnormalities. The prevalence for PKU is (26 cases, 6.62%) and it is more common in boys (Pozo et al., 2021). “Phenylketonuria was found in 11 provinces, with Cotopaxi in the Andes Mountains having the greatest prevalence” (Pozo et al., 2021). The report makes the case that the NBS program's scope has to be expanded in a few provinces and highlights the need of giving each step of the program enough time and attention to detail. Each illness was distributed differently among the provinces, with notable geographic diversity and greater relative incidence in several of the eastern provinces. 393 confirmed instances in all were recorded (Pozo et al., 2021). The research also advises that, in order to increase program effectiveness, the best diagnostic techniques and tools should be regularly assessed. Finally, the study emphasizes the complexity of genetic and ethnic diversity and how it influences disease incidence rates. Phenylketonuria was less common than the global norm, however it was more prevalent in some provinces than others. Based on the available evidence, the amount of newborn who were tested through the NBS program, there is still a 30% of children who haven’t been tested for these medical conditions. This demonstrated that

there is still a necessity for children to undergo testing for uncommon illnesses. During a case study of an Ecuadorian 15-year-old adolescent who got a late diagnosis at 3 years and 11 months old, the patient had seizures, severe mental retardation, a musty odor, and hypopigmented hair (De Lucca et al., 2017). There is a clear need for more investigation in Ecuador. Hene, the importance of this research.

Observational Research & Objective

This study's objective is to evaluate the intelligence and executive function of Ecuadorian kids between the ages of 2 and 17 who have been diagnosed with PKU. The USFQ Medical Department and Vanessa Romero, a specialist in genetics, metabolic problems, and uncommon diseases, selected the 20 individuals for the study. Participants must meet the following criteria in order to be included: they must be Ecuador residents, have a PKU diagnosis that has been confirmed in a laboratory, and be between the ages of 2 and 17. There will be no application of exclusion standards based on gender, race, education, or socioeconomic level. The WISC-V or WPPSI-IV will be used, depending on the participants' ages. IQ, verbal comprehension, working memory, fluid reasoning, visuospatial memory, and processing speed are the main characteristics of interest. Attention, language, memory, learning, sensorimotor skills, social perception, and visuospatial processing are secondary factors of interest. Tests will be administered by Ana Cacao, Priscila Navarrete, Valeria Troya, Nergiz Turgut, and Karen Larrea during the study's July 2023 session in Quito. Neuropsychologist Paloma Sotomayor will review the findings; she will be blinded to the study's goals. Socio-demographic questions will be asked of each participant's legal guardians. The participants and their legal guardians will also be asked for their informed consent for participation and data use. Each participant's test will take about 60 minutes to complete, and parents are required to accompany their children to the testing location. During

the testing session, which varies in length based on the participant's age group, data will be gathered in-person. Each psychometric test will be assessed for its psychometric validity when data collection is complete, and then Valeria Troya, Ana Cacao, Priscila Navarrete, and Karen Larrea will clean the data. A database will be used to store and analyze the psychometric results.

Methods

As it has been presented before, PKU has been detected to have a strong correlation with cognitive impairments and performance. Studies on children and adolescents with PKU showed lower performance on the Wechsler Abbreviated Scales of Intelligence in the reasoning, initiation of problem-solving, concept formation, inhibitory control, cognitive flexibility, and set shifting while there was a higher intake of Phe (VanZutphen et.al., 2007). Further investigation shows that a strict low PAH dietary treatment might prevent cognitive impairments. However, recent studies mention that even in cases where the diet has been applied in the first days after birth there is still a high incidence of attention-deficit–hyperactivity disorder and specific learning disabilities which differs from individuals without a diagnosis of PKU (Van Spronsen, et.al., 2021). Hence, there is a clear relationship between PKU and cognitive performance. Despite this, there is still research to be done to understand which are the areas and executive functions affected by PKU. In order to establish the association between the diagnosis of PKU and cognitive performance, the aim of this study is to determine the IQ and executive functions of children between the ages of 2 and 17 who were officially diagnosed with PKU. This will be evaluated through the use of psychometric tests, such as the WPPSI IV, WISC V and the NEPSY II. The advantage with the WPPSI IV relies on the versions of the test which are adapted to the ages of the participants; therefore there is the option of WPPSI IV for ages (2:6 - 3:11) and WPPSI IV

for ages (4:0 - 7:7). The WPPSI IV (2:6 - 3:11) contains full scales in the verbal comprehension, visual spatial scale and working memory scale; as well as ancillary index scales in verbal acquisition, nonverbal scale and general ability scale (Weschler, 2012). The WPPSI IV (4:0 - 7:7) will provide information about the children's working memory, verbal comprehension, fluid reasoning, visuospatial memory, and processing speed through two neuropsychological studies (Weschler, 2012). Both will provide an accurate intelligence quotient (IQ) scores of children in the cognitive areas mentioned before. In addition, the other Wechsler test that will be used is the WISC V which has a range of ages (6:0-16:11). In this latest version of the test, there have been additional subtests which add to the visual spatial scale, working memory scale and the fluid reasoning scale (Weschler,2014). Meanwhile, the NEPSY II "is a comprehensive instrument designed to measure neuropsychological development" (The Psychological Corporation, 2012) where the results inform a possible diagnosis and help the creation of an intervention planning. The neuropsychological functions measures provide information about attention and executive functioning, language, memory and learning, sensorimotor domain, social perception, visuospatial processing. Unlike the WPPSI IV, the NEPSY II is a psychometric test that can be tailored from the ages of 3 up to 16. All the assessments above provide the information needed to create a well-rounded report on the children's cognitive abilities and identify the possible intellectual disabilities.

Discussion

Due to the fact that the preliminary data will be available in July 2023 the following discussion is based on research for PKU. A loose low-phe nutritious diet is linked to cognitive decline, behavioral problems, as well as levels of anxiety and depressive symptomatology. This is in agreement with other studies on the subject, which have demonstrated that while maintaining a healthy diet does not always cure PKU, it does

significantly reduce the prevalence of many psychiatric illnesses. However, because this study will exclusively concentrate on children, it may improve our knowledge of the prevalence, diagnosis, and care of this illness in countries in Latin America. Given that there is a low prevalence of neonatal metabolic screening in Ecuador (due to factors primarily related to socioeconomic status and public health), it is anticipated that the cognitive manifestations of this disease will vary significantly in terms of the severity of their level of occurrence when compared to other studies on cognitive development in children with PKU. This is due to the greater likelihood of a late diagnosis in this research's group.

Risks

The participants' possible dangers include getting tired while waiting for their turn. If they decide they no longer desire to play with the age-appropriate toys supplied, this may occur. Frustration is another potential concern, as they can reach a point in the cognitive test when they are unable to move further and the test would terminate there. The propagation of COVID-19 is also taken into consideration, notwithstanding the minimal chance of the subsequent scenario.

Limitations

This is a multidisciplinary study, since it involves doctors, biologists, educational and neuropsychologists. It is one of this investigation's strengths, but it could also be a struggle for future research. In addition, participant recruitment specifically for children, since there could be issues with secure parental permission and governmental or institutional regulations. Similarly, time restraints could become a struggle, since researching takes a lot of time and demands patience and commitment. Time limits and other difficulties in conducting research might result from researchers having to juggle various tasks. It is uncertain if our findings

may be applied to other regions in Ecuador, due to the relatively small sample size and geographic restriction of our study.

Despite these drawbacks, our study offers crucial insights into PKU's impact in Ecuador, especially on children. To validate these results and investigate potential processes behind the observed relationships, more investigation is required. However, our study highlights the significance of studying cognitive impairments in metabolic diseases and encourages additional research in this area.

Suggestions for further research

The participants for this study have all been diagnosed with PKU and have followed the restricted low-Phe diet. However, it remains unclear if they are accurately executing the stated actions. Therefore, future studies could inquire more about the nutritional diet and other demographic variables. This research is very specific, in a country where there is lack of investigation in the topic; therefore it is expected to have many subsequent studies. Some suggestions for further research include performing a longitudinal study where there is a follow-up with participants over time. This could offer further information about the long-term characteristics of the Ecuadorian population with PKU. Also, conduct a more in-depth study with different research methods, more extensive in terms of the participants or the variables it examines. Finally, this research could potentially impulse psychoeducational programs about NBS in Ecuador.

Conclusion

PKU is a complicated phenomenon that requires more research since it impacts a wide range of effects on a person's life, including but not limited to cognitive, social, economic, and lifestyle factors. The gathered information offers important insights into the executive functions that children with diagnoses struggle with and can be used as a starting point for further research. Overall, this study will advance the knowledge of the IQ scores of PKU-affected children and adolescents in Ecuador and emphasizes the need for more investigation and study in this field.

People with PKU should adhere to a strict diet, to prevent adverse effects on their physical and mental functioning. Postnatal screening for PKU is essential to detect afflicted individuals early and treat them with a particular diet to prevent issues with cognitive development. However, there is a significant problem with postnatal screening for PKU in Ecuador because of a variety of factors, including socioeconomic status and restricted access to the necessary testing. Understanding how PKU impacts children's cognitive development in the country is crucial.

Studies have shown that people with uncontrolled or late-detected PKU frequently exhibit psychological traits that are primarily linked to the functioning of the frontal brain, such as lower IQ, difficulties with attention retention, and deficits in inhibitory control, especially in young people (Canton et al., 2019). PKU in kids has also been connected to traits of autism and ADHD (De Jaco et al., 2017). IQ is the factor that pops up most frequently in PKU research since it is a significant predictor of a child's academic and problem-solving aptitude

(Canton et al., 2019). It is important to keep in mind that most of these trials involve children who had postnatal screening and consumed a specific PKU diet. Conversely, children who receive a diagnosis later in life may experience serious effects on their mental development (Herenger, et.al., 2019). Executive functioning and IQ have a significant role in academic and personal success. Executive skills have been demonstrated to be a reliable predictor of academic achievement for children between the ages of 6 and 12 (Cortes et al., 2019). IQ has also been connected to socioeconomic success and has a favorable correlation with academic performance (Kriegbaum, 2018 as cited in Strenze, 2006). PKU may thus have a significant impact on the lives of the afflicted children if it has a negative impact on IQ and executive function. Given the lack of understanding surrounding the psychological traits of children who are diagnosed with PKU later in life, it is imperative to look into these factors in order to better understand their effect. Such study can identify any early childhood and adolescent developmental impairments and assist in determining the particular type of psychiatric care that these children may require. This study therefore has the potential to shed additional light on potential PKU-related deficits and pave the way for future research to create therapy and psychoeducational programs.

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