University of Missouri
University of Missouri

ARTIFACTS

A Journal of Undergraduate Writing

Sickle-Cell Disease Contributes to Cognitive Impairment in Children

Acacia C. Grimes

Acacia is from St. Louis, MO and graduated from MIZZOU with a bachelor of Health Sciences in May 2015 and is now pursuing a bachelor of Nursing Science from the University of Missouri Accelerated Nursing Program. In elementary school, Acacia had a friend who suffered from sickle cell disease that inspired her interest in researching the effects the disease has on the cognitive development of children. That interest led to her to report of the systemic effects that resulted from the disease as well as interventions that could be used. The article was intended to educate the public and reflect the information so it would be insightful.

Abstract

An examination of how sickle-cell disease contributes to cognitive impairment in children. The definition, classification, and pathophysiology of sickle-cell disease is discussed to support the cognitive impairment seen within children with sickle-cell disease. The quality of life that children with sickle cell experience is also discussed as it plays a role in how children with sickle cell experience the disease. Therapeutic measures are also examined to discuss the possible interventions that can be taken to aide children with sickle cell manage the disease. After careful research, it is concluded that four factors directly cause compromised neurological function in children with sickle-cell disease; (1) recurrent micro infarction of the central nervous system; (2) chronic hypoxic damage to the brain or diminished pulmonary function; (3) sub-acute brain damage that occurred during bouts of hypoxia associated with events such as aplastic crisis, acute chest syndrome, and obstructive sleep apnea; and (4) chronic nutritional deficiency associated with increased metabolic demands. The therapeutic interventions that are discussed to aid in the management of sickle-cell disease are inhibition of hemoglobin S polymerization and reduction of the intracellular hemoglobin concentration.

Keywords: sickle-cell disease, children, therapeutic interventions, cognitive impairment, quality of life, health related quality of life

Introduction

Sickle cell disease of the blood that attacks the red blood cells can is prevalent in predominately ethnic minorities in the United States. Children who suffer from this condition have many health-related as well as social and emotional complications associated with this disease. One of the most interesting and devastating health-related complications that can occur is cognitive impairment. Lack of adequate oxygen and blood supply to the brain as well as brain infracts (strokes) can contribute to the prevalence of cognitive impairment seen within children who have sickle cell disease. Apart from the loss of childhood freedoms from being brought in and out of hospital rooms, extensive tests, transfusions and treatments these children also face a great deal of pain coupled with cognitive impairment and decreased health-related quality of life. However, there are many therapeutic interventions that can affect the quality of children with sickle cell lives in a positive way.

Classification & Pathophysiology

Sickle-cell disease is a "multisystem disease, associated with episodes of acute illness and progressive heart damage, it is also one of the most common monogenic disorders worldwide" (Rees, Williams, & Gladwin, 2010, p. 2018). Sickle-cell disease derived its name from the sickle-shaped erythrocytes that James B. Herrick discovered in 1910. There are three major types of sickle-cell; (1) the most common form is homozygosis for the b^S allele, (2) hemoglobin SC disease (HbSC) which coinherits the b^S and b^C alleles and (3) HbS/b-thalassemia which occurs when b^S is inherited with a b–thalassemia allele. Our bodies produce 20 amino acids and four nucleic bases, which constitute for "standard" genetic code and "normal" functioning of body systems. Sickle cell is caused by a mutation in the b-globin gene in which the 17^{th} nucleotide is changed from thymine to adenine and the sixth amino acid becomes valine instead of glutamine. This mutation causes the affected red blood cells' nucleus to crystallize, grow and fill the erythrocyte, disrupting its structure and flexibility and promoting cellular dehydration, which

creates sickled cells. The sickled cells can block blood and other nutrients from travelling through veins and arteries causing pain and loss of blood to the brain, organs and extremities.

One of the main problems of sickle-cell disease in children is the development of cerebrovascular disease and cognitive impairment. Recurrent episodes of vaso-occlusion (pain) and inflammation result in damage to most organs, including the brain, kidneys, lungs, bones, and cardiovascular system, which become apparent with increasing age. This is viewed as a serious deficit in children because it not only leads to many health related problems, such as irreversible damage to organs as well as ischemic (restriction of blood supply and shortage of oxygen and glucose to cellular metabolism) injuries of the limbs, bowel, cutaneous tissues and even the heart and brain, which can result in death.

Cognitive Impairment

There are many factors that can contribute to the cognitive impairment of children with sickle cell disease. In *Abnormalities of the central nervous system in very young children with sickle cell anemia* (Wang, et al., 1998, p. 140) 39 children between the ages of 7 and 48 months were examined with magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA). The results showed that very young children with sickle cell anemia have infarction in the brain and/or stenosis of major cerebral arteries, similar to those reported in older children and even adults. The study indicated that lesions of vascular stenosis and brain ischemia occur in the first few years of life even in neurologically asymptomatic patients. Additionally, three patients experienced strokes with lesions, which are usually associated with abnormalities in adults with sickle cell disease.

This shows that seizures can be prevalent in the younger population contributing to loss of cognitive ability from strokes emphasizing the association of this symptom with significant pathologic conditions of the central nervous system, whether related to neonatal hypoxia or ischemia from vaso-occlusion. One report from this study addressed the possibility of developmental delay in preschool children with sickle cell disease. However, two of the six patients with abnormal imaging study results had Mental Developmental Index (MDIs) below 80 (at risk or delayed mental development), suggesting a need to look for further correlations among brain imaging, developmental testing, and neurologic history. This shows that whether the decrease in development is caused from neonatal hypoxia or ischemia from vaso-occlusion, it is still a relevant problem in association with cognitive impairment in children with sickle cell disease.

In another study, further evidence of cognitive impairment in children with sickle cell disease can be seen in an extensive study of 373 patients with varying classifications of the disease (255 with hemoglobin SS and 118 with hemoglobin SC). The participants were given a series of neuropsychological tests such as Wechsler Intelligence Scale for Children (WISC-R or WISC-III) and the Woodcock-Johnson Math and Reading Achievement Tests, Full-scale IQ (FSIQ) for complete cognitive capacity and a MRI. The researchers found that “children and adolescents with SCD between 6 and 18 years of age have a significant deficit in neuropsychometric performance associated with silent infarction and a significant decline in performance with age in certain areas” (Wang, et al., 2001, p. 395).

The control group was matched from 4 to 16 years of age. The mean FSIQ scores of the control group were between 87.3 and 94.3 with an average of 90. At a mean of about 12½ years of age, the children with sickle cell disease had average FSIQ scores of 84.8 (normal MRI findings) and 77.2 (silent infarct detected by MRI), which were slightly lower than the scores of the control group. Nine percent of 10-year-old children with hemoglobin SS (without infarcts detected by MRI) had FSIQ scores <70 (<70 constitutes for mild retardation). This demonstrates that children with sickle cell disease coupled with silent infarcts do present cognitive complications in their complete cognitive capacity specifically in verbal comprehension, perceptual reasoning and working memory. This shows the need for effective interventions to prevent this cognitive complication.

Furthermore, the study also found the four factors could come into play to explain the neurological deficit seen within these children; (1) recurrent micro infarction of the central nervous system; (2) chronic hypoxic damage to the brain or diminished pulmonary function; (3) sub-acute brain damage that occurred during bouts of hypoxia associated with events such as aplastic crisis, acute chest syndrome, and obstructive sleep apnea; and (4) chronic nutritional deficiency associated with increased metabolic demands. The effects of recurrent micro infarcts, chronic hypoxemia, and repeated tissue ischemia are likely to accumulate, directly resulting in compromised neurocognitive function.

Health Related Quality of Life: Functional Disability in Everyday Activities

Pain is a common consequence of sickle cell disease (SCD). Pain in the form of vaso-occlusive episodes can begin as early as 6 months of age and can be both frequent and severe. Pain can be associated with an increased impairment in daily activities such as school and play as well as potentially impairing adjustment in physical, emotional, recreational, educational, and vocational activities in daily functioning. In *Daily Functioning and Quality of Life in Children With Sickle Cell Disease Pain*, "depression significantly accounted for variance in both parent and child functional disability assessments. Family socioeconomic conditions were significantly independent predictors of health-related quality of life (HRQOL) in physical HRQOL, psychosocial HRQOL, and child-reported functional disability.

At the neighborhood/community level economically distressed neighborhoods independently contribute to decreased functional outcomes" (Palermo, 2008, p. 838). This shows that family socioeconomic factors are significant predictors of functional outcomes demonstrating that family income (SES) can cause social stress on the child contributing to lower physical activity and depressive nature. At the neighborhood and community level one can see the family SES and neighborhood socioeconomic distress was predictive of physical activity and healthy emotional development.

The processes by which neighborhood conditions may influence health outcomes are probably multifaceted. For example, the combined effects of SCD pain and low SES on school attendance may limit opportunities for recess and physical education, reducing physical HRQOL. Moreover, economically distressed neighborhoods are likely to be associated with economically distressed schools, which may lack the financial resources to provide playground equipment, physical education, and extracurricular activities. Therefore, children with sickle cell disease who live in low economic

status neighborhoods may be at increased risk for diminished physical HRQOL due to lack of engagement in physical activity.

In *Health-related Quality of Life in Children and Adolescents With Sickle Cell Disease*, a questionnaire was administered to 124 children and adolescents (ages 8 to 18 years with SCD (100 sickle cell anemia, 24 sickle b-zero thalassemia) and their parents analyzing the scores for children's and parents' ratings of overall HRQOL and psychosocial health and subscale scores for physical, emotional, social, and school functioning were compared with data from healthy children. The study used The PedsQL 4.0 to measure opinions or attitudes about problems related to physical, emotional, social, and school functioning pertaining to the impact that the child's illness may have on the family such as school days missed by the child or work days missed by the parent, number of days in the hospital, and ER visits.

It was found that both children with SCD and their parents, perceived overall HRQOL and all HRQOL subdomains to be lower than scores reported in healthy children. Dale states, "a large proportion of children with SCD would be 'at risk' for impaired overall HRQOL, as well as physical health and school functioning. by expressing lower mean scores than those of healthy children" (Dale, et al., 2011, p. 213). Management of the quality of life for children with SCD of these can be difficult to deal with and can create heightened anxiety and reduced confidence. In future research, providing psychosocial interventions such as assistance with schoolwork, counseling, or play therapy may contribute to increasing the quality of life for children with sickle cell disease.

Therapeutic Interventions

There are many physical complications caused by sickle cell disease. However, acute chest syndrome is the most prevalent and perhaps the most uncomfortable for those with SCD. Acute chest syndrome (ACS) is an important cause of morbidity and mortality in sickle cell disease (SCD). The Cooperative Study of Sickle Cell Disease prospectively followed 3,751 patients enrolled from birth to 66 years of age for ACS. There were 1,722 ACS episodes in 939 patients. Young children (age 2 to 4 years) presented with fever and cough, and rarely had pain. Acute chest syndrome (ACS) is the second most common cause of hospitalization in patients with sickle cell disease (SCD) and is responsible for up to 25% of deaths.

The frequency of presenting symptoms was age-dependent with fever and cough being more common in young children (age 2 to 4 years) and the incidence of chest pain, shortness of breath, chills, productive cough, and hemoptysis increasing with age. This is significant because even though young children do not initially experience pain, as they grow older they will experience all the symptoms that adults do. Therefore, since there is no cure for sickle cell disease and the complications that come with the disease, it is important to intervene to make the quality of life for children with SCD better by not having to experience pain associated with acute chest syndrome.

In *Acute Chest Syndrome in Sickle Cell Disease: Clinical Presentation and Course*, Elliott P. Vichinsky states, "presenting symptoms during a patient's first episode of ACS were predictive of symptoms during subsequent events. Knowledge of previous symptomatology should allow for earlier diagnosis and intervention in subsequent episodes" (Vichinsky, et al., 1997, p.10). This intervention policy could be used to help monitor children with SCD as early as two to four years of age to decrease their chances in

the future for developing moderate to severe acute chest syndrome. Telfer (2011) states, early intervention is important and should include, "Antibiotics (pneumococcal and atypical pneumonia cover), careful IV fluid maintenance, to prevent dehydration and avoid over-hydration, effective and safe analgesia, bronchodilators and transfusion" (p. 366). If ACS can be seen early and early interventions can be made, it is possible that children with SCD and ACS may not experience pain.

Furthermore, a number of independent approaches to therapy have been proposed and developed to help reverse the sickling of cells and that could solve the physical pain associated with ACS. Two of these approaches have undergone thorough laboratory and clinical investigation: chemical inhibition of hemoglobin S polymerization, reduction of the intracellular hemoglobin concentration, and pharmacologic induction of hemoglobin F, which can aid in the management of symptoms associated with sickle cell disease in children.

Inhibition of Hemoglobin S Polymerization

Franklin Bunn (1997) states, "hemoglobin S polymer is an ideal agent would be readily absorbed through the gastrointestinal tract, circulate in the plasma without binding strongly to plasma proteins, readily penetrate the erythrocyte membrane, and bind strongly and specifically to hemoglobin S in a way that would inhibit polymerization" (pp. 765-766). This would essentially create a chain of blood cells that could carry blood through arteries and veins that could aid in vaso-occlusion in regards to blood flow and possible regeneration of the classic round erythrocyte. However, a large amount of drug would be needed to bind to the approximately 400 g of hemoglobin in patients with SS disease. Unfortunately, no antisickling drugs tested thus far have a ratio of efficacy to toxicity that is high enough to merit clinical use.

Reduction of the Intracellular Hemoglobin Concentration

It is also discussed in *Pathogenesis and Treatment of Sickle Cell Disease*, Progress has recently been made in the development of drugs that inhibit K+ (potassium) and water loss from SS red cells and thus cause a reduction in the intracellular hemoglobin concentration, which results in sickled cells. In a clinical trial, "low doses of clotrimazole treatment in five patients with SS disease resulted in a prompt and striking reduction in irreversibly sickled cells and an increase in intracellular K+, accompanied by a small increase in the hemoglobin concentration" (Bunn, 1997, pp. 765-766). This dose essentially increases potassium levels forcing sickled cells to shrink in size and encourage red blood cells to revitalize themselves. "Recently, administration of magnesium supplements in transgenic mice with sickle cell disease and in 11 patients with SS disease resulted in approximately 50 percent inhibition of potassium–chloride cotransport accompanied by a significant decrease in dense erythrocytes and an increase in the hemoglobin concentration" (De Franceschi, , Bachir, & Galacteros, 1997, pp. 1849-1851).

Conclusion

Sickle cell disease is a condition that causes many health related problems such as irreversible damage to organs, acute pain and ischemia of the extremities. Through careful research, it is concluded that children with sickle cell do suffer from cognitive impairment from; (1) recurrent micro infarction of the

central nervous system; (2) chronic hypoxic damage to the brain or diminished pulmonary function; (3) sub-acute brain damage that occurred during bouts of hypoxia associated with events such as aplastic crisis, acute chest syndrome, and obstructive sleep apnea; and (4) chronic nutritional deficiency associated with increased metabolic demands. These recurrent instances direct result in compromised neurocognitive function.

The quality of life that children with sickle cell disease is directly affected because of illness from the disease. Children that come from low socioeconomic communities and neighborhoods so do have the adequate resources to play and engage in physical activity, therefore, they are impacted physically, emotionally and socially. Moreover, children with sickle cell disease as well as their parents have self-reported lower health related quality of life in comparison to healthy children from extensive tests, illness, missed days of school/work and lack of physical activity and play.

Finally, therapeutic interventions such as chemical inhibition of hemoglobin S polymerization and reduction of the intracellular hemoglobin concentration have made fantastic strives in reversing sickled cells caused by the dehydration of regular erythrocytes. Inhibition of hemoglobin S polymerization has created a chain of blood cells that could carry blood through arteries and veins that could aid in vaso-occlusion in regards to blood flow and possible regeneration of the classic round erythrocyte while reduction of the intracellular hemoglobin concentration has focused on created potassium infused drugs to force sickled cells to shrink in size and stimulate red blood cells to revitalize themselves.

Professional Statement

In the case of sickle-cell disease and its prevalence in children, if I were asked to recommend a course of action for sickle-cell anemia in children I would call for interventions and early tests to administered so that the prevalence of the disease and its characteristics can been seen early and intervention methods can be designed. It is imperative that children born with sickle-cell disease are monitored throughout the first couple years of life. A course of action that I could design would include diagnosis of the disease at an early age. Second, medications would be administered to decrease the chances of the child creating complications such as seizures or hypoxia. There is little evidence that can support that this could be done, however, with close monitoring these symptoms could significantly be decreased. Third, it would be beneficial to continually educated children with sickle cell, even if they were in the hospital or at home. Monitoring neurological defects and consistent education could decrease the prevalence of cognitive impairment in children with sickle-cell disease. Fourth, it would be helpful to create an environment where children would be able to have physical activity that would not be too strenuous so that the children could get enough exercise. This aspect of the program could be multifaceted including gradual progress in physical activity to get the children to a “normal” level of physical recreation without damage to their bodies.

Reference List

Bunn, H. (1997). Pathogenesis and treatment of sickle cell disease. *The New England Journal of Medicine,* 337, 762-769.

Dale, J., et al. (2011). Health-related quality of life in children and adolescents with sickle cell disease. *Journal of Pediatric Health Care*, 25/4, 208-215.

De Franceschi, L., Bachir, D., & Galacteros, F. (1997). Oral magnesium supplements reduce erythrocyte dehydration in patients with sickle cell disease. *The Journal of Clinical Investigation*, 100/7, 1847-1852.

Palermo, T. (2008). Daily functioning and quality of life in children with sickle cell disease

pain: Relationship with family and neighborhood socioeconomic distress. *The Journal of Pain*, 9/9, 833-840.

Rees, D. C., Williams, T. N., & Gladwin, M. T. (2010). Sickle-cell disease. *Lancet*, 376, 2018-2031.

Telfer, P. (2011). Management of sickle cell disease: Acute episodes in the community and in hospital. *Paediatrics and Child Health*, 21/8, 363-368.

Wang, W., et al (1998). Abnormalities of the central nervous system in very young children with sickle cell anemia. *The Journal of Pediatrics*, 132/6, 994-998.

Wang, W, et al (2000). Neuropsychologic performance in school-aged children with sickle cell disease: A report from The Cooperative Study of Sickle Cell Disease.

***Part of* Issue 13**, *published in August 2015*

***Topics:* Health and Society**

About *Artifacts*

Artifacts is a refereed journal of undergraduate work in writing at The University of Missouri. The journal celebrates writing in all its forms by inviting student authors to submit projects composed across different genres and media.

Artifacts is sponsored by The Campus Writing Program.