

Review Article

Effects of Anemia on Cognitive Function

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DOI:10.18579/jpcrk/2017/16/2/116430

Received on: 03/02/2017

Revised on: 01/04/2017

Accepted on: 04/04/2017

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ABSTRACT

Purpose: To establish the relation between Anemia and cognitive function.

Approach: Published articles from Pubmed and other Internet sources were used to establish the relation between anemia and cognition.

Finding: There are various factors like RBC, hemoglobin and iron content which affects cognition indirectly. Whereas some factors such as defect in gene, directly affects the cognition.

Conclusion: Anemia not only affects the physical health, but also affects the mental health like cognition. RBC, hemoglobin and iron contents affect the cognitive function while due to defect in gene, causes anemia, which also affects cognitive functions. Cognition of infant is also affected by maternal anemia.

Keyword: Anemia, Cognitive function, RBC, Hemoglobin.

INTRODUCTION

The name Anemia is derived from Greek word (*anaimia*) meaning "lack of blood". It is a condition in which the blood hemoglobin level or number of red blood cells decreases from its normal level. Normal level of hemoglobin in man is 13-14g/dl and in woman it is 12-13g/dl¹.

Hemoglobin content varies with age, sex, altitude, smoking, and pregnancy status. Anemia develops when the rate of bone marrow red cell production falls to keep pace with destruction or loss of cells².

Due to decrease in the hemoglobin their oxygen carrying capacity decreases, is insufficient to meet the physiologic needs, Due to decrease in oxygen blood levels which are inadequate to support normal metabolism resulting in easy fatigue, paleness, shortness of breath, edema and chilliness that are often experienced by anemic individuals.

It is a symptom of some disorder rather than a disease³. In vertebrates, it shows common hematological condition associated with several conditions such as drug toxicity, parasite, genetic or acquired defects and blood loss⁴.

It has been observed that anemia is the greatest cause of death in developing countries⁵. Globally, it affects almost 1.62 billion people, which is almost one fourth of the world population¹. It has been observed that female are more affected(9.9%) than male(7.8%)⁶. According to the National Family Health Survey (NFHS)-(III), Approx 55 % women in India have anemia, including 39 % with mild anemia, 15 % with moderate anemia and 2 % with severe anemia⁷. It affects almost all age groups; the highest prevalence is in preschool-age children approx 47.4%⁸.

Types and causes of Anemia⁹

Based on their causes, anemia has divided into following classes:

Anemia due to nutrition deficiencies

There are various nutrients, which is required for the normal growth like iron, zinc magnesium.

Iron deficiency anemia

This is the most common type of anemia. This occurs because of the decrease in iron content in our body. For the production of RBC, Bone marrow needs adequate iron to synthesis hemoglobin. Without adequate iron, enough hemoglobin cannot be produced for red blood cells. Main causes of the decrease in the iron content is blood loss, such as from heavy menstrual bleeding, ulcer, cancer and regular use of some over-the-counter pain relievers, like aspirin.

Vitamin deficiency anemia

Various vitamins deficiencies also lead to the anemia. Along with iron, our body needs various vitamin B₁₂ and folate to produce enough healthy red blood cells. A diet lacking in these and other key nutrients can cause decreased red blood cell production. Some people may consume enough B₁₂, but are not able to process the vitamin. This leadsto vitamin deficiency anemia like

- a) Pernicious anemia: vitamin B₁₂ deficiency anemia, deficiencies in VitB₁₂ because of not enough intrinsic factor.
- b) Megaloblastic anemia: Decrease in folate concentration leads to megaloblastic anemia. Due to hypovitaminosis (deficiency of vitamins specially B₁₂ and/or folic acid) defect in the DNA synthesis of red blood cells occurs which results megaloblastic anemia.

Anemia of chronic disease

Some of the chronic diseases such as cancer, HIV/AIDS, rheumatoid arthritis, kidney disease, Crohn's disease and other chronic inflammatory diseases also interfere with the production of

red blood cells. A variety of diseases, such as leukemia and myelofibrosis, can cause anemia by directly affecting blood production in bone marrow.

- a) Aplastic anemia: decrease in the RBC production because of infections, certain medicines, autoimmune diseases and exposure to toxic chemicals.
- b) Hemolytic anemia: when the destruction of RBC is greater than production of RBC, because of certain diseases.

Inherited Anemia:

Some of the anemia is hereditary;it transfers from parents to offspring.

- Sickle cell anemia:It is caused by a defective form of hemoglobin that forces RBCs to assume an abnormal crescent (sickle) shapebecause of which the life span of RBC decreases.
- Fanconi's anemia: It is an autosomal recessive genetic disorder occurs due to defect in the protein, responsible for the DNA replication.
- Thalassemia: It is genetic disorder that transfers from parents to their offspring. Beta-thalassemia also known as Cooley's anemia or homozygous β -thalassemiais a hematological disorder characterized by defective erythropoiesis and peripheral hemolysis.

Cognitive Function

Cognition is a scientific term for thought processing of information orprocess of acquiring knowledge and understanding through thought, experienceand the senses¹⁰.

Cognitive function includes¹¹:

- **Perception:** Recognition and interpretation of sensory stimuli (smell, touch and hearing)
- **Attention:** Ability to sustain concentration on a particular object, action, or thought, and ability to manage competing demands in our environment.
- **Memory:** Short-term/ working memory

(limited storage), and Long-term memory (unlimited storage).

- **Language:** Skills allowing us to translate sounds into words and generate verbal output.
- **Visual and Spatial Processing:** Ability to process incoming visual stimuli, to understand spatial relationship between objects, and to visualize images and scenarios.
- **Executive Functions:** Abilities that enable goal-oriented behavior such as the ability to plan, and execute a goal. These include
 - a) Flexibility:** The capacity for quickly switching to the appropriate mental mode.
 - b) Theory of mind:** Insight into other people's inner world, their plans, their likes and dislikes.
 - c) Anticipation:** prediction based on pattern recognition.
- **Problem-solving:** Defining the problem in the right way to then generate solutions and pick the right one.
- **Decision making:** The ability to make decisions based on problem-solving, on incomplete information and on emotions (ours and others)
- **Working Memory:** The capacity to hold and manipulate information "on-line" in real time.
- **Emotional self-regulation:** The ability to identify and manage one's own emotions for good performance.
- **Sequencing:** The ability to break down complex actions into manageable units and prioritize them in the right order.
- **Inhibition:** The ability to withstand distraction, and internal urges.

part of brain involved in cognitive function⁵³

a) Prefrontal Cortex: Involves in planning and evaluating outcomes and consequences of actions and events. Personality traits and appropriateness of behavior in a social context are also expressed through this area.

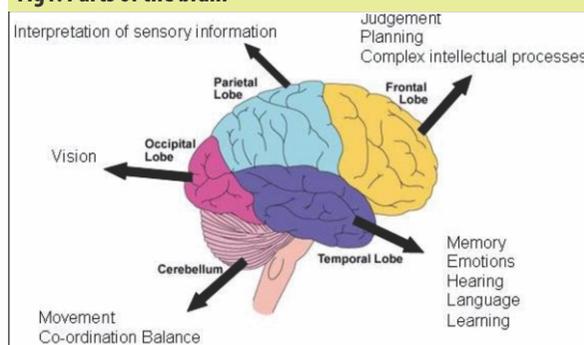
b) Frontal Lobes: Right frontal lobes are centre for language and left frontal lobe mostly process nonverbal information.

c) Parietal Lobes: Processing of sensory information into a perception.

d) Occipital Lobe: This lobe involves in receiving and processing visual information.

Mechanism of cognition:

Fig1: Parts of the brain



Cognitive development is an adaptive effort to various environmental influences. This is accomplished in the following two ways¹².

- **Assimilation:** Incorporating new thoughts, behavior and objects into the existing structures.
- **Accommodation:** Changing the existing structures in response to new challenges.

Process of cognitive development¹³

During process of cognitive development, assimilation and accommodation are the main process which is intermediated by different processes. Assimilation is applying the existing thought to the new situation if that idea is not sufficient. It causes disequilibrium and then a new idea is added to attend the equilibrium which is called accommodation. Equilibrium is the natural tendency of human to stay in the stable form. It drives the learning and the process of cognition continues.

Stages of development

In 1980, A Swiss psychologist proposed the theory of



cognition. According to him the developmental stages are divided into four parts-

a) Sensorimotor stage: It extends from birth to 2 years of age. Object permanence comes in this stage which means an object still exists even if it is hidden.

b) Pre-operational stage: It extends from 2 years to 7 years. During this stage children are able to think about symbolic things.

c) Concrete operational stage: 7 years to 11 years. Children start thinking logically, means start working things internally in their head.

d) Formal operational stage: 11 year and The following are some of the main biological factors

Hereditary aspects

Genetics play a major role in cognitive development. Children actually inherit their intelligence from their parents. Many scientists have the opinion that it is not possible to control intelligence and cognitive development because these are pre-determined by hereditary factors.

Age and Gender

Attention and memory decreases with the age¹⁴. Aging slows the speed of processing of information that might be because of lack of inhibitory control. Female sex hormone (estrogen) and male sex hormone (testosterone) both enhances the cognitive function in similar ways¹⁵. Females are good in verbal fluency, perceptual speed, accuracy and fine motor skills, where as males are good in spatial, working memory and mathematical abilities¹⁶⁻¹⁷.

Nutritional factors

It has also proven that nutrition plays an important role in developing cognition. Women who do not consume enough amounts of protein during their pregnancies have chances of decreased cognitive function in kids. This is because proteins play an

important role in the development of the brain¹⁸.

Sensory organs

Sensory organs are important in cognitive development. This enables children to recognize things and people around them. Children with disabilities in sensory organs develop cognitive abilities more slowly as compared to those who are normal.

Environmental factors

Environmental factors are the external influences that affect cognitive development. These are mostly controllable. They include:

- Economic factors.
- Family and society.

Interrelation between Anemia and Cognitive Function

Anemia affects cognition by both direct neuro chemical effect and by indirect effect on behavior. Direct neuro chemical effect by which anemia affects cognition is due to the defect in normal oxidative metabolism in the brain. The indirect mechanism is by iron deficiency anemia, which affects the cognition¹⁹.

Indirect methods

There are various ways by which anemia indirectly affects cognition. They are:

RBC

Red blood cells are one of the components of blood. RBCs are disc like shape which carries hemoglobin, a metallo-protein, made up of heme and globin protein and carries oxygen and transport oxygen to various sites.

The process of formation of RBC from bone marrow is called erythropoiesis, main hormone in erythropoiesis is EPO, the P300 component of the EPO reflects attention and memory processes. Various

studies have reported, there is a change in P300 components of erythropoietin, as the age changes, there is an abnormal P300 values have been observed in demented patients²⁰.

The membrane of RBC fatty acid composition reflects the dietary fatty acid intake. Membrane omega-3 fatty acid composition is more biologically stable than plasma concentrations²¹, since the lifespan of RBC is up to 120 days whereas the plasma concentration reflects intake over only the last few days²². Long-chain omega-3 polyunsaturated fatty acids (PUFA) are abundant in the brain, particularly the omega-3 PUFA DHA and the n-6 PUFA arachidonic acid; both essential fatty acids are synthesized from dietary precursor α -linolenic acid and linoleic acid, respectively²³.

Measurement of RBC fatty acid composition is a reliable biological indicator of dietary intake of omega-3 PUFAs. A longitudinal study relating RBC PUFA levels with cognitive performance showed that lower concentrations of omega-3 PUFA were associated with a higher risk of cognitive decline in an elderly²⁴. Anevidence has been established that biosynthesis of EPA and DHA from their precursor α -linolenic acid appears to decrease with age²⁵. A recent clinical trial found that daily supplementation with DHA in older adults for 24 weeks improved learning and memory function²⁶.

Hemoglobin

In a cross-sectional studies in older community-dwelling populations have revealed an association between low hemoglobin and cognitive function²⁷⁻²⁸.

Because of low blood hemoglobin, there is a decreased oxygen supply to the brain. In Moderate–Severe anemia there is a decreased performance on tests of recent memory, working memory, and fine motor speed²⁹.

Iron

Decrease in hemoglobin means decrease in iron content. It also has been observed that iron deficient individual are lethargic and suffers from malaise, they find difficulties in performing the task. Various treatment trials have showed an association between

iron treatment and measures of lassitude³⁰ and memory³¹. Iron is a necessary part of brain tissue. Decrease in the iron concentration in the brain causes a reduction in the neurotransmitter levels like epinephrine, dopamine and 5-HT which are required for cognitive function. In case of anemia, there will be impaired neurotransmitter functions, leading to hypomyelination and delayed neuromaturation thus lowering the cognition¹⁹. Nerve impulses move slower when iron deficiency occurs. Iron deficiency during infancy may cause permanent damage to the child's brain. Iron deficiency during the first two years of a child's life is associated with behavior changes and delayed psychomotor development. Enough, but not too much, is the key to appropriate iron intake³².

Over the past decades, a considerable literature has been published on the association between iron status/anemia and cognitive development in children, as well as in animal models³³. It is believed that iron is involved with different enzyme systems in the brain, including the cytochrome c oxidase enzyme system in energy production, tyrosine hydroxylase for dopamine receptor synthesis, delta-9- desaturase for myelination, and fatty acid synthesis, and ribonucleotide reductase for brain growth regulation³⁴⁻³⁷. In addition, iron appears to modify developmental processes in hippocampal neurons by altering dendritic growth³⁸⁻³⁹.

Direct Methods

There are various studies that show direct relationship between anemia and cognition.

Aplastic/Fanconi's anemia

Aplastic anemia is caused by bone marrow failure while Fanconi's anemia is an autosomal recessive genetic disorder. Fanconi's anemia is a congenital form of aplastic anemia which occurs due to defect in a protein responsible for DNA repair⁴⁰. It is a rare inherited disease characterized by bone marrow failure because of defects in the bone marrow. Individuals with Fanconi's anemia have lower than normal numbers of red and white blood cells and platelets. The lack of white blood cells predisposes the

patient to infections, while the lack of RBCs can lead to anemia. Anemia can cause fatigue as a result of low levels of oxygen being delivered throughout the body. Low platelet levels in Fanconi's anemia may cause problems with blood clotting which is necessary to stop bleeding and repair the site of injury or surgical incision. There are 19 genes for Fanconi's anemia, mutations in any of 19 genes lead to birth defects, cognitive impairment, bone marrow failure-related blood disorders, cancers that include pediatric leukemia, premature aging, and other abnormalities⁴¹. Patients with Fanconi's anemia may have an intellectual disability or learning disabilities associated with improperly formed nerve connections in the brain. Individuals who have Fanconi's anemia are often smaller in stature, have a low birth weight, grow at a slower rate than normal, and take longer than normal to develop skills, such as walking and reading.

Hemolytic Anemia

In Hemolytic anemia, the destruction of RBC is faster than its synthesis. Hemolytic anemia is caused by the heterozygous mutations of the gene for erythrocyte isozyme of aldolase, ALDOA (Arg303X)⁴².

Aldolase a homotetrameric protein encoded by the ALDOA gene, converts fructose-1,6-bisphosphate to dihydroxy acetone phosphate and glyceraldehyde-3-phosphate. Aldolase mainly present in red blood cells and skeletal muscle is necessary for the production of adenosine triphosphate (ATP) in erythrocytes. Aldolase A deficiency has been reported as a rare, autosomal recessive disorder. Hemolysis has been associated with this disorder in patients, with myopathy and mental retardation.

Sickle Cell Anemia

Sickle cell anemia involves an altered gene that produces abnormal hemoglobin. RBC with sickle hemoglobin has too little oxygen due to its C-shape and becomes stiff and sticky. The normal life span of RBC is 120 days but the life span of sickle celled RBC is 10-20 days. New findings suggest that cognitive impairment can also be present in patients with sickle cell disease who are free of focal brain

damage⁴³. Cognitive impairment in children with sickle cell disease may be a function of chronic hypoxia of the brain⁴⁴. There are many factors that can contribute to the cognitive impairment of children with sickle cell disease. Lack of adequate oxygen and blood supply to the brain as well as brain infarcts (strokes) can contribute to the prevalence of cognitive impairment seen within children who have sickle cell disease. In one study it has been observed 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 adults. Even in the first few years of neurologically asymptomatic patients lesion of vascular stenosis and brain ischemia occurs. Some adult patients who have sickle cell disease may develop cognitive problems such as having difficulty organizing their thoughts, making decisions or learning even if they do not have severe complications such as stroke related to sickle cell disease. According to NHLBI Acting Director Susan B. Shurin, M.D. sickle cell disease patients scored lower on measures such as intellectual ability, short-term memory, processing speed, and attention⁴⁴. Studies of brain function in children who have sickle cell disease have suggested that some children with the disease have experienced silent brain injury. Others without obvious changes on brain scans may have some level of cognitive dysfunction that seems to worsen with age. Stroke is a common complication of sickle cell disease and can lead to learning disabilities, lasting brain damage, long-term disability, paralysis or death.

Thalassemia

Beta-thalassemia major is a serious life-limiting and potentially life-threatening condition⁴⁵ which occurs due to deficiency in the synthesis of beta-globin chains of hemoglobin.

Patients with beta thalassemia major, particularly those showing signs of hemosiderosis, had significantly impaired function in all neuropsychological tests. One study found significant intellectual impairment in a group with thalassemia major. Beta-thalassemia major causes substantial disruption in education and social activities⁴⁶. This study also found that many of these patients suffered

from sadness, anger and loneliness. This might be due to the chronicity of the disease state that influences patient's recreational activities, capabilities and peer as well as family relationships, culminating in anxiety, secluded behavior and depression⁴⁷⁻⁴⁸.

It's not only thalassemia major which affects cognition, but it is found that patients with thalassemia minor also have prolonged latency and reduced amplitude as compared to the normal⁴⁹.

Pernicious Anemia/Megaloblastic⁵⁰

Pernicious anemia and Megaloblastic anemia occurs due to decrease in vitamin B12 and folate concentration respectively. Vitamin B12 deficiency can cause neurologic damage, which can be irreversible if it continues for long periods without treatment. Folic acid supplements are standard for pregnant women and women who plan to become pregnant. Folic acid reduces the risk for birth defects of a baby's brain and spine spina bifida and anencephaly.

Newly established link between anemia and mild cognitive impairment⁵¹

In a large population-based study of randomly selected participants in Germany, researchers did a case control study and found that participants with anemia, showed lower performances in verbal memory and executive functions.

Low hemoglobin level may contribute to cognitive impairment via different pathways. Study has reported mild cognitive impairment to occur almost twice more often in participants diagnosed with anemia.

Cognitive impairment in neonatal with maternal anemia⁵²

It is known that the growth of neonatal depends on mother's condition. It has seen that even mild iron deficiency in the mother reduces iron stores in the fetus, resulting in a neonatal iron-deficient condition.

Perinatal iron deficiency also affects brain and cognitive development, because dendritic growth, synaptogenesis, and glial cell proliferation and the brain growth start from the last one-third of

pregnancy and continues to the first 2 years after birth. Total brain volume doubles the first year and reaches 80–90% of adult volume by age two. This phase of rapid growth represents a sensitive period.

Neurogenesis occurs in the hippocampal dentate gyrus which is also persists in the neonatal period and throughout adulthood. One recent studies has showed the evidence that neurogenesis occurs in different cortical regions, including the prefrontal cortex in human infants¹⁸.

In one study, perinatal iron deficiency to newborn temperament-like behaviors showed that Perinatal iron deficiency or infant whose mother were iron deficient had higher levels of irritability in infants. In other studies, lower levels of neonatal Hemoglobin and serum iron (and ferritin to a lesser degree) showed higher levels of negative emotionality and lower levels of alertness and soothability^{54,55}.

CONCLUSION

Anemia is a very common blood disorder mainly related to the physical health but it also affects mental health like cognitive function directly and indirectly. Due to decrease in oxygen supply to brain there is reduction in performance. Anemia is associated with nutrition and diseases affecting mental health. The indifference towards anemia as a disease is a matter of concern and therefore people should be aware about the effect of anemia on cognitive function. People especially pregnant women and kids should be concerned about their diet. Since mother's health is directly linked to fetal growth, dietary supplements have to be incorporated to overcome anemia.

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