Neurological Manifestations of Hemoglobinopathies

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INTRODUCTION
Hemoglobinopathies are inherited single gene disorders that in most cases are autosomal co-dominant traits.

These are divided into two main groups as follows: (a) Thalassemia syndromes (b) Structural hemoglobin variants (abnormal hemoglobins). Both are caused by mutations and/or deletions in the α- or β-globin genes. When gene defects cause Hb synthesis disorders, this gives rise to thalassemia. Hemoglobin structure in these cases is normal. When they because changes in Hb structure, this gives rise to abnormal hemoglobin. There are also many mixed forms that combine features of both groups, e.g. β0/β+-thalassemias, HbSC disease and HbE α-thalassemias [1].

The clinical manifestations depend on the number of the type of globin chain affected. The Thalassemia represents the most common monogenetic disorder worldwide. Thalassemia is a genetic blood disorder in which the body makes an abnormal form of hemoglobin, the protein in red blood cells that carries oxygen. Hemoglobin is made of two proteins from four globin genes and two β-globin genes. There are two types of thalassemia: α-thalassemia and β-thalassemia depending on which globin genes are affected. α-thalassemias are caused by a β-globin chain synthesis defect. At the molecular level, they result from partial (α+) or total (α0) deletions, or more rarely mutations, of one or more of the four α-globin genes (αα/αα). They occur mainly in Africa, Arab nations, and, more frequently, South-East Asia [1] β-thalassemia syndromes are the result of insufficient (β+) or absent (β0) production of β-globin chains. Their molecular causes are β-globin gene mutations. Hematological changes become manifest from between the ages of three months and six months onwards [2]. A last group is made up of rare haemoglobin variants. They result from mutations only observed in a few families or individuals. These latter are divided into the following four well-defined groups: (a) Variants with a tendency to aggregate and with sickle cell formation, e.g. the sickle syndromes (b) Variants with abnormal hemoglobin synthesis, e.g. HbE (c) Variants with a tendency to precipitate and with hemolysis (unstable hemoglobins), e.g. Hb Köln (d) Variants with abnormal oxygen transportation and congenital polycythemia, e.g. Hb Johnstown or with congenital cyanosis (abnormal methemoglobins, HbM abnormalities, e.g. M lwate). The forms in the third and fourth groups cause serious illness when heterozygous. When homozygous, they are fatal [3-6]. The term “sickle-cell disease” in dudes all manifestations of abnormal HbS levels (proportion of HbS >50%). These include homozygous sickle-cell disease (HbSS) and a range of mixed heterozygous hemoglobinopathies (HbS/β-thalassemia, HbSC disease, and other combinations) [7,8]. HbS is the most dangerous of all hemoglobinopathies. The sickle cells caused by a lack of oxygen lead to vascular obliterations, so infarctions with tissue death can occur in almost all organs (skin, liver, spleen, bone, kidneys, retina, CNS). Chronic hemolytic anemia can usually be well tolerated. This hemoglobinopathy arises from the substitution of the amino acid glutamine by the valine in the sixth position of beta globin chain. SCD is characterized by hemoglobin polymerization, erythrocyte stiffening, and subsequent vaso-occlusion. Supportive care is the hallmark of current treatment for sickle cell anemia, and blood transfusions and iron chelation therapy the standard treatment for β-thalassemia. Drugs that increase fetal hemoglobin production are used in sickle cell anemia. Oral iron chelators have been useful in both disorders [8-10].

Neurological manifestations in thalassemia
The b-thalassemias are a group of autosomal recessive disorders characterized by absence or reduced synthesis of the red cell b-globin chains. The terms thalassemia major (TM) and thalassemia intermedia (TI) lack specific molecular correlates, but encompass a wide spectrum of clinical, as well as laboratory abnormalities [1]. Over the years, several reports have demonstrated involvement of the nervous system in β-thalassemia patients. In most cases, these complications
remained subclinical and were detected only during neuropsychological, neurophysiological, or neuroimaging evaluation. Cognitive impairment, abnormal findings on evoked potentials, complications due to extramedullary hematopoiesis, cerebrovascular disease, and peripheral neuropathy comprise the broad spectrum of neurological involvement.

**Extramedullary hematopoiesis**

Extramedullary hematopoiesis (EMH) is a non-neoplastic proliferation of hematopoietic tissue outside the bone marrow and peripheral blood that is typically a reaction to various hematologic disorders that result in abnormal bone marrow production or function [11]. The incidence of EMH in patients with TI may reach up to 20% compared to polytransfused TM patients where the incidence remains <1% [12]. A paraspinal location for the hematopoietic tissue occurs in 11–15% of cases with EMH [13]. More than 80% of cases remain asymptomatic and the lesions are usually discovered incidentally by MRI. CT and MRI findings provide information that lead to clinical decisions [14]. A review of the literature revealed 23 other cases of symptomatic spinal epidural EMH. Eighty-eight percent of the patients were males. Symptoms lasted longer than 1 week in 90% of cases, and 91% demonstrated incomplete neurological deficits [15, 16].

Clinical presentations including: back pain, paraesthesia, paraplegia, ankle clonus, spastic gait, exaggerated or brisk tendon reflexes, Babinski response, or urgency of urination and bowel incontinence [16].

The extramedullary masses are diagnosed [17, 18] by MRI as an intense epidural lesion on both T1- and T2-weighted images, compressing severely the spinal cord. After administration of a paramagnetic agent, an intermediate enhancement of the masses is present. Management strategies have included radiation, laminectomy, transfusion therapy and hydroxyl urea or a combination of these therapies; some patients treated with systematic transfusion have improved [19]. Radiation therapy has been reported to yield excellent results. Hematopoietic tissue is sensitive to radiation in conservative doses of (750–3500 cGy), is non-invasive, avoids the surgical risks of potentially severe hemorrhage and incomplete resection, and has a high complete remission rate in the majority of patients. Relapse rates are moderate (37.5%), but retreatment provides excellent chance for second remission [19, 20].

Hyper transfusion therapy has been used as a first-line treatment method, with complete neurologic recovery [21]. However, hypertransfusion therapy is not free of complications (iron overload, alloimmunization etc.), and these should be kept in mind and avoided when possible. Furthermore, hyper transfusion therapy can be both diagnostic and therapeutic at the same time because only edema and cord compression secondary to extramedullary hematopoiesis respond to this treatment method [22, 23]. The combined use of transfusions and hydroxyl urea showed a good response in some cases [24, 25].

**Stroke**

One complication in patients with β-thalassaemia who had prolonged survival is chronic hypercoagulable state, attributed to a number of factors, including the procoagulant activity of damaged circulating red blood cells (RBCs), co-inheritance of coagulation defects, depletion of antithrombotic factors, endothelial inflammation and conditions that increase thrombotic burden which results in thromboembolic events involving major organs including the brain [26]. Logothetis et al., reviewing 138 cases of beta-thalassaemia major (B-TM) in Greece and described a stroke syndrome in 2 patients and transient ischemic attack in about 20% of the cases [27]. In Italian multicenter study of 735 patients with B-TM reported 16 thromboembolic events with presentation of headache, seizure, and hemiparesis [28] Iron deposition in combination with inflammatory and immunogenic factors is involved in the pathophysiology of cardiac dysfunction in these patients. The relationship of iron overload effect on brain ischemia and infarction in beta-thalassaemia major was evaluated in some articles and in southern Iran a higher frequency (66%) was reported for silent cerebral infarctions in transfusion-dependent patients with beta-thalassaemia major [29]. Heart failure and arrhythmias, caused by myocardial siderosis, are the most important life-limiting complications of iron overload in beta-thalassaemia patients. Cardiotoxicity seems to be the cause of stroke in cases of β-thalassemia major [30–32]. In splenectomized patients, there is a higher number of circulating pathological RBC and an increased number of activated platelets. There are numerous data that show a significant association between increased number of activated platelets with thromboembolic phenomena and a high incidence silent infarcts [33]. Silent brain infarction refers to cerebral infarcts detected by brain imaging in subjects without any related clinical manifestation which are radiologically similar to lacunar infarcts [33–35]. Available studies indicated a high prevalence of silent infarcts in patients who are adults, transfusion-independent, splenectomized, and have a platelet count >500 x10/L. Studies conducted on larger and more heterogeneous groups of TI patients with careful stratification will allow better SCI risk-assessment and evidence based screening recommendations [31, 36, 37]. Several scattered case reports actually describe the occurrence of overt strokes in TI patients with moyamoya syndrome [38]. Management of stroke in thalassemia is still controversial and clear guidelines have not been established [39]. Transfusion therapy to prevent rather than treat complications, including thromboembolic disease, in combination with effective iron chelation therapy seems to be effective [40]. Although prophylactic antithrombotic therapy has been suggested for patients with β-thalassaemia intermedia at risk for thrombotic complications, such as post surgery, during pregnancy and immobilization, the results of long-term follow-up studies are currently unavailable.

**Chelation neurotoxicity**

There are three major iron chelators used in thalassemia namely Desferrioxamine, Deferiprone and Deferasirox. Of the three Desferrioxamine has been extensively studied for neurotoxicity. The chelator desferrioxamine (DFO) has been used since the late 1960s to increase iron excretion and hence reduce iron overload. Auditory neurotoxicity under long-term DFO treatment has occasionally been reported.

Porter et al. [41], found a significant correlation between therapeutic index (mean daily DFO dose divided by serum ferritin level)
level) and risk of sensorineural hearing loss in thalassemic patients. It has been suggested [42], that chelation of metals other than iron (perhaps copper) could have been responsible for the ocular toxicity of high-dose intravenous DFO.

**Neurocognitive dysfunction in thalassemia**

The use of intense therapy has increased the life expectancy of patients with β-thalassemia, as well as the frequency of complications [43]. Anemia, which leads to hypoxia and iron deposition, leads to brain damage in the long term. High iron deposition in the putamen, caudate nucleus, and motor and temporal cortex of patients with β-thalassemia have been described. These areas are as important for cognitive function as for implicit and explicit memory. Neuropsychological tests reliable for diagnosis of cognitive impairment in β-thalassemia major patients, and they may even facilitate early diagnosis have been used in several studies [44].

In the majority of studies on neurologic complications in β-thalassemia, reported that the neuropsychological studies available revealed a considerably high prevalence of abnormal IQ, not correlating, however, to factors such as hypoxia or iron overload. They proposed that factors associated with severe chronic illness, rather than the disease per se, could be responsible for these findings. Such factors include regular school absence due to transfusions and frequent hospitalizations, physical and social restrictions resulting from the disease and its treatment, abnormal mental state due to the awareness of being chronically ill, and, last, the overly protective family attitude that leads to restricted initiative and psychosocial development [45,46].

**Sickle cell disease**

Sickle cell disease (SCD) is a hemolytic anemia caused by the presence of hemoglobin S (Hb S) in homozygous, named sickle cell anemia (SCA), or associated with thalassemias and other hemoglobin variants. Phenotypic expression of the SCD is variable and depends on the associated genotype and other factors that alter the hemoglobin concentration or the blood flow [47]. In general, the homozygous inheritance is the most severe form of the disease [48,49]. The beta-globin gene cluster haplotypes associated with Hb S (βS-haplotypes) are potential modulators of the disease [48,49]. The beta-globin gene cluster haplotypes generally, the homozygous inheritance is the most severe form and depends on the associated genotype and other factors that alter the hemoglobin concentration or the blood flow [47]. In general, the homozygous inheritance is the most severe form of the disease [48,49]. The beta-globin gene cluster haplotypes associated with Hb S (βS-haplotypes) are potential modulators of the disease [48,49]. The beta-globin gene cluster haplotypes associated with Hb S (βS-haplotypes) are potential modulators of the disease [48,49].

**Headache**

Children and adolescents with sickle cell disease (SCD) have a high prevalence of recurrent headaches (24.0–43.9%) [50]. Acute presentation with headache can be diagnostically challenging, as the clinician must consider evaluation of several potentially devastating conditions including vascular diseases (stroke, hemorrhage, venous sinus thrombosis, moyamoya, posterior reversible encephalopathy syndrome), facial and orbital bone infarcts, dental pain, and osteomyelitis. A study by Niebanck et al. [51], demonstrated an overall prevalence of frequent headache in children with SCD at a major US medical center of 32.4%, similar to that of all ethnically matched control subjects, but significantly higher in children younger than 13 years [52]. A similar study demonstrated that 24.5% of Nigerian children and adolescents with SCD reported frequent headaches, significantly higher than healthy control subjects in that population. Additionally, acute headache represents 0.5% to 1.2% of total Emergency Department (ED) visits in the general pediatric population [53]. Platelet counts also were significantly higher during the acute headache presentation of SCD-SS patients with acute CNS events, and a trend toward significance was observed in white blood cell elevation from baseline in patients with acute CNS events. These data are consistent with the well-described proinflammatory and procoagulant environment observed in sickle cell disease [8].

**Stroke**

Stroke (or cerebrovascular accident) is one of the common complications of severe sickle cell disease (SCD). Stroke was defined as an acute neurologic syndrome caused by vascular occlusion or hemorrhage, with resultant ischemia and focal neurologic symptoms or signs lasting more than 24 hours; transient ischemic attacks (TIAs) were episodes lasting less than 24 hours. The Cooperative Study of Sickle Cell Disease found that 24% of individuals with SCA experienced a clinical stroke by age 45 years [54].

The type of stroke may be due to different pathophysiologic mechanisms or to progressive cerebrovascular damage. The notion that infarctive strokes occur more commonly in children whereas hemorrhagic strokes occur more frequently in adults is supported partly by this study. Infarctive stroke was more common in SS patients less than 20 years of age than in those older, but patients more than 30 years of age were also at risk. The period of lowest risk for infarctive stroke (20 to 29 years of age) was the period of highest risk for hemorrhagic stroke [55].

Ischemic stroke is a common brain injury. The most common intracranial vessels affected are the distal internal carotid, proximal middle cerebral, and anterior cerebral arteries. The vasculopathy of these large vessels is most often associated with cortical infarction. Factors associated with infarctive stroke included the following: prior TIA, history of meningitis, increased systolic blood pressure, increased steady-state leukocyte count, the 2-week period following acute chest syndrome, increased rate of acute chest syndrome, and low steady-state Hb level [56-58].

Clinical symptoms and signs include hemiparesis, monoparesis, aphasia or (dysphasia), seizures, severe headache, cranial nerve palsy, stupor, and coma [59-61].

MRI findings are classified without CNS pathology as normal (no CNS pathology), cerebral infarction, atrophy, and cerebral infarction and atrophy [52,53,56,57].

Clinical management in the acute period is empiric. Red cell transfusion to lessen the anaemia, reduce tissue hypoxia and reduce the percentage of HbS is the mainstay of treatment. Manual or automated exchange transfusion, when available, is often employed in the initial management. The goal is to reduce the % HbS to < 30% of the total haemoglobin and to raise the haemoglobin level to about 10–12g/dL. Chronic transfusion therapy is the most effective known method to reduce recurrences of stroke. The initial goal of transfusion therapy is to
Neurocognitive dysfunction in sickle cell disease

SCA has become a chronic illness associated with progressive deterioration in quality of life. Global neurocognitive impairment was observed in patients with overt strokes, but neurologically intact children also had impaired neurocognitive function that increased with age. Children with sickle cell disease suffer impairment of cognitive function [65]. Declining IQ scores, learning difficulties, and impairment of executive function were common in children with normal findings on imaging studies. Silent infarcts frequently involve frontal lobe lesions, resulting in deficits in attention and executive skills. These cognitive deficits likely lead to learning difficulties because of poor sustained attention, self-organization, and problem-solving skills [66-68].

The majority of adult patients with SCA found to have lower neurocognitive performance associated with hemoglobin level, age, and education. Previous studies have consistently found reduced hemoglobin levels to be a risk factor for neurocognitive dysfunction in individuals with SCA as well as the general population. To our knowledge, the Vichinsky study is the first comprehensive assessment of neurocognitive function in neurologically intact adults with SCA. The major findings are that (1) adults with SCA showed poorer performance on neurocognitive tests when compared with community controls; (2) anemia is associated with the age-related decline in cognitive performance; and (3) MRI findings do not explain the performance differences in the subset of patients with neuroimaging studies, despite the presence of more lacunar infarcts in patients than in controls [67-69]. As with most chronic diseases, depression and other psychiatric disorders are common in SCD. Patients with cerebellar dysfunction may struggle with depression and other forms of psychological distress, limitations in cognitive ability and flexibility, slowed reaction times and impaired attentional modulation, as well as less ability to do “multitasking” automatically. These important aspects of higher order behavior have an impact on quality of life, employment, and personal relationships and need to be recognized by the medical profession as well as by patients and their families [69,70].

Analgesic dependence/mental disorders

SCD pain can be as intense as post-operative pain (Walco & Dampier, 1990), and severe painful episodes are treated in hospital with parenteral opiates, usually intramuscular injections or intravenous infusions of pethidine, morphine or diamorphine [71]. Among the most common complaints by patients is that staff unjustly suspect or accuse patients of drug dependence, and this is borne out to some extent by surveys of hospital staff.

Delirium and confusional [72-74] states are among the most common mental disorders encountered in patients with chronic medical illness. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day. Delirium is fairly common among hospitalized patients, with around 1 in 10 having a period of delirium. In SCD it often exhibit tolerance to opioids, and analgesics due to repeated use of these agents. This results in the need for higher and higher doses of opioids to provide the same level of analgesia. Chronic use of pethidine and other opioid agonists may result in an increased sensitivity to pain, which may develop within a month of initiating chronic opioid therapy.

As with most chronic diseases, depression and other psychiatric disorders are common in SCD. Psychosis is a symptom of neuropsychiatric disorder [73]. It is experiencing things and believing them to be real when they are not; Children with SCD are often underweight, shorter than normal children, and have delayed puberty. With their small stature, adolescents with SCD encounter problems with self esteem, dissatisfaction with body image, and social isolation, with participation in athletics also limited due to fear of initiating a vaso-occlusive crisis. School performance suffers when hospitalizations lead to missing multiple school days. Accordingly, adolescents often experience hopelessness and social withdrawal.

Comprehensive management of patients with SCD should include adequate social support, appropriate education about illness and improved communications among health care providers [74,75].

OTHER MANIFESTATIONS

CNS Infections in thalassemia and sickle cell disease

Splenectomy function is lost when the spleen has been surgically removed, is congenitally absent, has atrophied following repeated infarction (eg. sickle cell disease), or following splenic artery thrombosis [76]. Asplenic patients and those with impaired splenic function are at risk for a fulminating sepsis syndrome usually due to Streptococcus pneumoniae. The terms “postsplenectomy sepsis” and “asplenic sepsis” are largely interchangeable since the functional defects are the same regardless of whether the causative process is congenital or acquired. Despite the widespread availability of pneumococcal and Haemophilus influenza vaccines and the general use of penicillin prophylaxis, individuals with hemoglobinopathies remain at risk for invasive infections from pneumococcus and other organisms. Prior to the availability of H. influenza type b and pneumococcal vaccines, young children (below five years of age) with SCD in the United States had a 13 percent risk of developing bacterial sepsis or meningitis with mortality rates of 30 and 10 percent in patients with sepsis and meningitis, respectively [77-79]. Although mortality has significantly decreased since the introduction of vaccines, particularly since licensure of the conjugate pneumococcal vaccine (Prevnar) in 2000, approximately one-quarter of deaths between 1999 and 2002 in children with SCD in the first nine years of life continue to be due to infectious causes [79]. CNS infection may present as a medical emergency, and it is essential need for empiric therapy with third-generation cephalosporins and vancomycin for all patients with meningitis while awaiting results of culture and susceptibility testing [80-82].

Masked megaloblastic anemia

The occurrence of anemia in Thalassemic patients is who developed folic acid or vitamin B12 deficiency is usually unknown [83]. Microcytosis may mask folate or vitamin B12 deficit. Moreover, inthalassemic heterozygotes that develop
anemia, the possibility of megaloblastic pathogenesis should be pursued even when the RBC indices maintain their microcytic-hypochromic expression. The first abnormality is usually sensory impairment, most often presenting as distal and symmetrically paraesthesiae of the lower limbs and frequently associated with ataxia. Almost all patients demonstrate loss of vibratory sensation, often in association with diminished proprioception and cutaneous sensation and a Romberg sign. Corticospinal tract involvement is common in more advanced cases, with abnormal reflexes, motor impairment and, ultimately, spastic paraparesis. A minority of patients exhibit mental or psychiatric disturbances or autonomic signs, but these rarely if ever occur in the absence of other neurological changes [84].

Even though almost all Thalassemic patients are supplemented with folic acid, prevention with vitamin B12 supplements should be considered.

REFERENCES
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