

Review article

Neurological complications in β -thalassemia

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Abstract

Over the years, several reports have demonstrated involvement of the nervous system in β -thalassemia patients. Neurological complications have been attributed to various factors such as chronic hypoxia, bone marrow expansion, iron overload, and desferrioxamine neurotoxicity. In most cases, neurological involvement does not initially present with relevant signs or symptoms (i.e., is subclinical) and can only be detected during neurophysiological or neuroimaging evaluation. Abnormal findings in the visual, auditory, and somatosensory evoked potential recordings are mainly attributed to DFO neurotoxicity. On the other hand, nerve conduction velocity abnormalities are associated either to chronic hypoxia and older age or to hemosiderosis, whether by means of pancreas involvement or not. Neuropsychological studies available reveal a considerably high prevalence of abnormal IQ, not correlating, however, to factors such as hypoxia or iron overload. It is proposed that factors associated to 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. As life expectancy for β -thalassemia patients extends, the use of neurophysiologic and neuropsychologic monitoring becomes imperative, enabling early detection of neural pathway impairment and allowing for appropriate management, in order to achieve a better life quality for this patient group.

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1. Introduction

β -Thalassemia, a relatively common condition in Mediterranean and South-East Asia regions, was first described in the 1920s. It is the most severe form in a diverse group of genetic disorders of hemoglobin synthesis, in which life can only be sustained by regular blood transfusions [1]. Although transfusion therapy prolongs survival, the absence of a physiological iron excretion mechanism leads to uneven accumulation of this metal in various body organs. Iron deposition principally affects the heart, liver, and endocrine glands and results

in death, usually during the second decade of life, if patients are left untreated [2]. Heart failure remains the commonest cause of death even in well-managed thalassaemic patients, with a reported mortality incidence of 50% before the 35th year of age in some centers [3]. Therefore, life-long chelation therapy is an essential facet in the management of β -thalassemia patients, extending their survival, while dramatically improving their quality of life. Desferrioxamine (DFO), a parenterally administered iron chelator, has been in use for over 30 years; during this period its benefits and limitations have been clearly defined. New diagnostic and therapeutic advances, such as magnetic resonance imaging (MRI), a sensitive, non-invasive method for measuring body iron content allowing for early detection of hemosiderosis prior to organ dysfunction establishment [4], as well

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as the clinical use of oral iron chelators that allow better treatment compliance, are expected to further improve survival rates and life quality for thalassemic patients.

2. Neurological complications in β -thalassemia

Over the years, several reports have demonstrated involvement of the nervous system in β -thalassemia patients. Neurological complications have been attributed to various factors such as chronic hypoxia, bone marrow expansion, iron overload, and desferrioxamine neurotoxicity. In most cases, neurological involvement does not initially present with relevant signs or symptoms (i.e., is subclinical) and can only be detected during neurophysiological or neuroimaging evaluation.

2.1. Hypoxia

In poorly managed thalassemics or patients suffering from non-transfusion dependent thalassemia (thalassemia-intermedia), chronic anemia results in extramedullary hematopoiesis. The formation of extramedullary hematopoietic foci is slow and initially subclinical. Symptoms eventually result from a mass effect that leads to compression of surrounding structures, including cranial and peripheral nerves. In this context, narrowing of the optical canal with subsequent optic neuropathy and visual failure has been described as a rare complication [5,6]. Similarly, conductive hearing loss resulting from extramedullary hemopoiesis of the middle ear has been reported in thalassemia patients [7]. More frequently described are cases concerning paravertebral masses causing spinal cord or cauda equine compression. The presentation and severity of such cases vary from mild motor and sensory symptoms to complex paraplegia, *sphincter disturbance and impotence*. Clinical awareness is important for early diagnosis and prevention of irreversible neurological complications. Magnetic resonance imaging is the radiological method of choice for diagnosing extramedullary hematopoietic masses and delineating the extent of spinal cord involvement [8]. Treatment in such cases is controversial; therapeutic strategies include hypertransfusion, radiotherapy, use of hydroxyurea, surgical decompression by means of laminectomy, or various combinations of the above [9–14].

Prolonged nerve hypoxia may also result in axonal sensorimotor neuropathy, as stated in a report by Stamboulis et al. [15], where a sensory axonal polyneuropathy was present in 19 out of 36 evaluated beta-thalassemia patients (52.7%) and significantly correlated to patients' age and hematocrit level.

Hypoxia due to chronic anemia has also been suggested to play a role in the development of ischemic

stroke, a well-described, though infrequently reported complication of β -thalassemia. Incorpora et al. [16] report a 3% incidence of hemorrhagic stroke in a population of 300 thalassemic children. The incidence of brain damage is higher in non-treated patients with thalassemia-intermedia and increases with age, however, lesions seem to be generally small and single in this patient group [17]. It should be noted that multiple factors, besides hypoxia, are known to be involved in the hemorrhagic and thrombotic complications occurring in thalassemic patients. These include post splenectomy thrombocytosis, insulin dependent diabetes mellitus, estrogen-progestin treatment, and atrial fibrillation [18]. Additionally, profound hemostatic changes such as low S and C protein level, enhanced platelet consumption and ongoing platelet, monocyte, granulocyte, and endothelial activation are observed in thalassemics, leading to a hypercoagulable state [19–24]. Whatever the underlying cause, stroke can present with silent progression, therefore patients should be closely monitored for potential development of such a complication. MR imaging is a useful tool in identifying patients at risk for clinical stroke, so that they can be properly managed.

2.2. Hemosiderosis

The effect of iron on neural pathways in thalassemic patients was initially connected to sensorineural hearing loss resulting from cochlear siderosis [25]. The use of newer neurophysiologic methods, such as evoked potentials, enabled detection of subclinical neurological complications, partly attributed to the toxic effect of iron overload [26].

More recently, the use of magnetic resonance imaging demonstrated the presence of iron on brain structures, such as the cortex, putamen, and caudate nucleus [27]. Since several studies indicate increased iron deposition in the basal ganglia of patients suffering from diseases like Alzheimer's and amyotrophic lateral sclerosis [28,29], the clinical implications of brain MRI findings in thalassemic patients remain speculative, especially as their life expectancy is now increasing.

With regards to cognitive defects, relevant literature in patients with β -thalassemia is limited and non-conclusive, however, iron overload seems to be – at least partly – responsible for such complications. In a study by Monastero et al. [30] thalassemic patients were significantly impaired on all neuropsychological tests compared to controls, in particular those demonstrating signs of hemosiderosis.

Finally, glucose metabolism impairment resulting from pancreas siderosis, is an important additional factor related to complications involving the central and/or peripheral nervous system in β -thalassemia patients [31].

2.3. DFO neurotoxicity

Regular chelation therapy with DFO has been shown to produce negative iron balance, reduce tissue iron stores, delay or prevent iron-induced organ damage and improve survival in patients with transfusional iron overload. DFO remains the chelator more widely used to treat patients with β -thalassemia worldwide, despite compliance limitations due to the lifelong need for parenteral administration. However, DFO treatment is not adverse-event-free. High dose regimes, or even standard regimens applied to well-chelated patients with minimal iron burdens, have been associated with neurotoxicity. Various possible mechanisms for DFO associated neuropathy have been suggested, such as multiple trace element chelation, metalloenzyme activity inhibition, and oxygen based free radical generation [32–34]. However the case may be, DFO toxicity is possibly related to patient individual susceptibility and, therefore, is unforeseeable and not easy to prevent [35].

The observed neurological abnormalities primarily involve the visual and auditory pathways [36–39]. They are dose-related and, in most cases, reversible following temporary drug cessation or dose modification [40]. In one of the earliest reports, Orton et al. [41] describe two thalassemic siblings experiencing visual loss secondary to DFO toxicity. Following drug discontinuation, one of the reported siblings showed almost complete optic neuropathy reversal, while the other had a permanent unilateral visual loss. Regarding DFO ototoxicity, a long-term audiological evaluation reported by Kontzoglou et al. [42] demonstrated the presence of high frequency sensorineural hearing loss in 20.2% of assessed patients, with subsequent clinical improvement or aggravation inhibition, in the majority of cases, following temporary treatment discontinuation or dosage reduction. The findings are consistent with relevant literature, indicating the causative role of DFO, even when administered in dose regimens that are considered non-toxic [43]. It is of interest to note that, in some cases, ocular and auditory abnormalities may be sub-clinical, therefore, only detectable using neurophysiological laboratory testing [44,45].

Management of thalassemia patients presenting with DFO neurotoxicity is difficult. In patients who are asymptomatic or demonstrating mild electrophysiological changes, dose reduction with serial monitoring is recommended [46]. In symptomatic cases or cases showing electrophysiological deterioration, temporary drug withdrawal with careful re-administration in lower doses is suggested.

In addition to the well-established ocular and auditory DFO toxicity, chelation treatment has been associated with peripheral neuropathy in thalassemia patients [47,48]. The relevant clinical presentation includes parasthesias, myalgias, and muscle weakness,

although subclinical involvement detectable during neurophysiologic evaluation has been reported [49,50].

2.4. Nutrition deficiency

There have been conflicting reports in relation to the levels of certain vitamins and trace metals in the blood of thalassemic patients, their deficiency state known to be associated with nervous system pathology.

It has been well documented that the spinal cord, brain, optic nerves, and peripheral nerves may be affected by B12 deficiency. B12-related neuropathy has been reported in thalassemia patients, though probably incidentally [51]. In contrast, early literature on thalassemia offers evidence that in inadequately treated patients folic acid deficiency is common [52,53]. Folic acid deficiency is less frequently seen in well-transfused thalassemics, but is still an important problem in those with the intermediate forms of the disease [54].

Increased zinc and copper fecal and/or urinary excretion, possibly related to or exacerbated by iron chelation treatment, has been demonstrated in certain studies [33,55–57]. However, other reports have shown that trace element depletion is minimally associated with neurological complications [49], while others have failed to confirm abnormal blood trace element levels in thalassemic patients [31].

To date, the clinical significance of various nutritional deficiencies has not been defined, therefore, further evidence from prospective studies is needed.

3. Neurophysiology–neuropsychology

3.1. Evoked potentials and β -thalassemia

Evoked potentials (EP) denote a non-invasive neurophysiological method of evaluating the central nervous system (CNS). They have been widely used in the diagnosis of demyelinating diseases, whereas references on their use in assessing thalassemic patients are recorded by the mid 1980s [58]. Although not specific for a particular disease, EP are sensitive tools in detecting subclinical CNS lesions.

Abnormal findings in the visual (VEP) and auditory (BAEP) evoked potential recordings are mainly attributed to DFO neurotoxicity, their incidence varying from 6% to 32% and 0% to 25%, respectively [31,44,45,49]. With regards to somatosensory evoked potentials (SEP), reports on thalassemia patients are limited. Wong et al. [31] describe abnormal SEP findings in 4 out of 34 study cases (11.76%), two of which were complicated by diabetes mellitus, a fact significantly correlating to somatosensory neural pathway impairment.

3.2. Nerve conduction velocity and β -thalassemia

Literature concerning nerve conduction velocity (NCV) studies in thalassaemic patients remains limited. Abnormal findings are associated either to chronic hypoxia and older age [59] or to hemosiderosis, whether by means of pancreas involvement or not [28]. Reported incidence of pathological NCVs is quite similar in all reports, reaching a percentage of approximately 20% [28,50,59].

3.3. Neuropsychology and β -thalassemia

Neuropsychology evaluates cognitive functioning using standardized psychometric tests, however, literature regarding thalassaemia patients is extremely limited. The first study to evaluate multiple cognitive domains, a report by Monastero et al. [30] reveals significant differences between study patients and controls and suggests the potential role of hemosiderosis in impaired cognitive functioning. The sole other report using standardized neuropsychometric testing – the Weschler Intelligence Scale for Children (WISC) [60] – reveals a considerably high prevalence of abnormal IQ (36.36%), not correlating, however, to factors such as hypoxia or iron overload [50]. It is proposed that factors associated to severe chronic illness, rather than the disease per se, could be responsible for the study 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.

4. Conclusion

As life expectancy for β -thalassaemia patients extends, the use of neurophysiologic and neuropsychologic monitoring becomes imperative, enabling early detection of neural pathway impairment and allowing for appropriate management, in order to achieve a better life quality for this patient group.

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