Neurological Deficits among Beta-Thalassemia Patients and its Possible Therapeutic Intervention: A Comprehensive Review

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ABSTRACT

Beta-thalassemia is a genetico-haematological disorder that affects the integrity, structure, and survival of red blood cells due to deleterious mutation in the β-globulin chain of hemoglobin. Other than blood disorder, this condition gives rise to numerous neurological and haematophysiological conditions which have not been fully discussed yet. These conditions include extramedullary hematopoiesis, evoked potential (Sensory, Auditory and Visual), neuropathy and myopathy and predisposition to the hypercoagulable state leading to stroke. Moreover, most opted therapy to alleviate this condition intrigue neurotoxicity that requires clinician’s round the clock attention. Beta thalassemia remains an incurable disease, and various therapies have been introduced to fulfill the body’s blood requirement. But this condition implicitly gives rise to a damaging range of symptoms that cannot be overlooked. Therefore, our review encompasses all those anomalies associated with beta-thalassemia and its probable curative therapy.

Keywords: Beta thalassemia, Neurological deficits, Cognitive impairment, Extramedullary hematopoiesis, Evoked potential, Neuropathy.

On the other hand, imaging devices like magnetic resonance imaging (MRI) are employed to evaluate the iron chelation therapeutic effects based on signal intensity on T1 and T2 weighted sequences, as lower signal intensity suggests iron overload. Such intervention expedites the assessment of iron levels in the body before the onset of dysfunction of organs and hemosiderosis could set in. Many studies showed that beta thalassemia affects the neurological conditions of those individuals who suffer from this disease. However, these neurological anomalies have not been fully compiled or discussed yet. In this article, we will discuss these neurological impairments caused by beta-thalassemia and their possible curative therapy to alleviate some of these conditions.

EXTRAMEDULLARY HEMATOPOIESIS

Extramedullary hematopoiesis (EMH) is a homeostatic phenomenon that arises among chronic anemic patients in which hematopoietic foci are formed other than bone marrow to compensate the circulatory needs. In 1954, Gatto and their colleagues reported
the extramedullary hematopoiesis in the splenectomized patient presented with Cooley's disease and spinal cord compression. Extramedullary foci of hematopoiesis formations tend to be deliberate whose symptoms do not appear simultaneously. However, when the size of the foci starts to increase, causing the appearance of various nerve compressions, both cranial and spinal and peripheral in nature. To determine the severity of signs and symptoms, it is necessary to identify the location, size and type of nerve injury, and the degree of spinal cord participation. When cranial nerve compression progresses, it results in optic neuropathy, and visual impairment due to pinching of the optic canal, which rarely occurs.

Another rare complication associated with thalassemic patients is a loss of auditory perception when foci start to form in the middle ear. Paravertebral masses accumulation compresses either cauda equina or spinal cord which disrupts sensory and motor neurons signaling that results in sexual dysfunction, paresthesia, ankle clonus, paraplegia and loss of sphincter control. But these symptoms range from mild to intricate presentation when clinically assessed. Prompt diagnosis might prevent irreparable damage to the nervous system due to EMH subclinical nature.

**EVOKE POTENTIAL**

The evoked potential is a medical procedure used to evaluate the health of the brain and their nerve impulses. This technique is typically utilized for demyelinating diseases; meanwhile, it is also employed for thalassemia because it allows physicians to recognize subclinical lesions in the nervous system. Various studies revealed that deferoxamine (DFO) neurotoxicity interacts with the visual and auditory pathway of thalassemic patients.

Limited literature has been reported regarding sensory evoked potential (SEP) and nerve conduction studies among thalassemic individuals. However, neurophysiological studies done among thalassemic patients revealed aberrant results, SEP of two patients was aggravated by type II diabetes. These abnormal findings of various neurophysiological studies are linked with older age, hemosiderosis, DFO neurotoxicity, chronic hypoxia, or either with pancreas siderosis. Subclinical lesions in the central nervous system are hard to detect and diagnose. So, the evoked potential approach is generally utilized due to their high sensitivity and specificity to uncover neurological lesions.

**VISUAL EVOKED POTENTIALS (VEP)**

Studies have been reported that visual evoked potential values are altered from the normal range in beta-thalassemic individuals due to iron overload and on the other hand neurotoxicity due to DFO is another culprit which causes disrupted visual evoked potential according to some reports.

**BRAINSTEM AUDITORY EVOKED POTENTIAL (BAEP)**

From Wong's study, slight sensor-neural loss occurs which was seen in 15% of their patients while Triantafyllou et al. 1991 suggested that this abnormality is reversible when the treatment of DFO is stopped. Another interesting observation is put forward by Teli and their colleagues, where they found abnormal values of BAEP among thalassemia-intermedia patients.

**SOMATOSENSORY EVOKED POTENTIAL (SSEP)**

In the continuation of Wong's study, another neurological procedure was conducted to assess somatosensory evoked potential among thalassemic individuals. According to their report, a total of 12% of patients had increased subclinical cortical impairment either in their posterior tibial or median SSEP. This condition has also been reported in thalassemia-intermedia individuals by Teli et al study. In their report, they revealed that 4% of their thalassemic patients had aberrant values of somatosensory evoked potential, suggesting that this complaint is due to no blood transfusions and chelation therapy among these patients. Along with that, deteriorated somatosensory impulses and subclinical neurological lesions might be triggered by chronic anemia associated with coagulopathy co-morbid with hypoxia.

**NEUROPATHY AMONG BETA-THALASSEMIA VARIANTS MYOPATHY**

Myopathy is a neuromuscular disease that leads to dysfunctioning of muscle fibers causing muscle weakness. Myopathy among beta-thalassemia patients is common due to limited blood oxygen supply to muscular tissues. It was first reported by Logothetis and their colleagues in which they disclosed that lower limbs of thalassemic individuals had proximal weakness along with irregular electromyographic values.
Similarly, Nemtas et al, 2018 conducted electromyographic studies among 36 beta-thalassemia patients in which a total of 10 patients had myopathy alone while the other six had polyneuropathy accompanied by myopathy. 33-35 Both upper and lower extremities had aberrant electromyographic values along with proximal weakness in them.

PERIPHERAL NEUROPATHY

Peripheral neuropathy is a neuropathophysiological condition in which nervous stimulus (both sensory and motor in nature) from the central nervous system to peripheral nerves are disrupted due to the paucity of blood supply and prolonged hypoxia that aggravate demyelination and severely injure nerve fibers (axons). This event interrupts the appropriate signaling and working of peripheral nerves in bodily functions. Stamboulis et al. first introduced axonal sensorimotor neuropathy term., in 2004 which is described as reduced capacity to sense and move due to the damage done to axonal nerve fibers which disrupt the sensory-motor response of beta-thalassemic individuals. 33 Nerves which are especially affected among these individuals are peroneal and ulnar nerves. According to Stamboulis, this neuropathy results from low hematocrit level, that is worsened with increasing age and other pulmonary complications. According to Papanastasiou and their co-workers, they reported that 22% of their patients had peripheral neuropathic symptoms confined to motor nerve fibers. However, Zaferious study was contrary to Papanastasiou in which they revealed clinically that among 25% of their thalassemic patients had reduced sensory conduction velocity value followed by 10% of motor nerve impulses disruption. However, many studies indicated that sensory polyneuropathy rate has increased up to 78%. 33 Loss of essential nutrients or minerals, iron overload, drug-induced neurotoxicity, and chronic hypoxia due to severe anemia are the contributing factors behind this increased incidence of sensory polyneuropathy. An interesting finding of neurophysiological studies reported by Sawaya (2006) in which they suggested that symptoms of sensory neuropathy are more excessive in those who are suffering from intermedia condition. 35 Circulatory insufficiency, chronic hypoxia, and average age are the possible factors described by Sawaya and Stamboulis et al., which makes neuropathy aggravated in such patients. However, until now, there is no literature available to testify that peripheral neuropathy is more aggressive either in major or intermedia state. However, nerve conduction studies were considerably fine among those who had regular chelation and transfusion therapy. In around 76% of thalassemia patients, their quality of life affected due to peripheral neuropathy which negatively impacts their survival activities. 36 Various factors such as chronic hypoxia, average age irrespective of sex, iron overload, and drug induced neurotoxicity, are thought to be associated with the development of neuropathy. 37 Nevertheless, the main culprit behind this illness remains a question among clinicians.

STROKE

In both beta-thalassemia major and intermedia, the hypercoagulable state is the major risk factor resulting in thrombotic stroke due to an increased level of activated platelets and hemolyzed red blood cells that leads to the formation of thrombin. 30,38 This coagulable condition is triggered due to chronic anemia in thalassemic patients which leads to ischemic strokes (0.25–0.46%) rarely while 3% of cases result in hemorrhagic stroke. 39,40 In 1972, compatibility between transient ischemic attacks and a stroke syndrome was shown in about 28 out of 138 cases of beta-thalassemia. 40 Another study indicated that 2.2% of beta thalassemic patients were diagnosed with transient ischemic attacks with symptoms of hemiparesis, headache, and seizures. 39 Recently thromboembolic events have been witnessed in a mixed population with thalassemia intermedia and thalassemia major as reviewed in Nemtas review. 11 Large hemispheric territorial infarcts are evident in patients with beta thalassemic patients. 15,41-43 It is assumed that arrhythmias and siderosis induced cardiomyopathy incite cardioembolic stroke in these patients. 39,44,45 In thalassemia-intermedia patients, a cerebrovascular disease typically presents with asymptomatic ischemic lesions that affect profound brain structures except for cerebral cortex that remains unaffected. 45 According to Taher et al, study 36, thromboembolic disease, was the fifth most common complication, which affected 14% of the patient population. Splenectomy was also seen as a cause of silent cerebral infarcts in most of these affected patients. 46,47 To ameliorate the anemic condition, splenectomy could prevent thrombocytopenia and profound anemia that is associated with most of the clinical cases of severe splenomegaly. 43,48

CHELATION THERAPY NEUROTOXICITY

Chelation therapy regulates iron by preventing the
formation of hemosiderin in the vital organs, which increases the quality of life among thalassemic patients.\textsuperscript{34} However, many reports clearly indicated the adverse effects of therapy in which principal among them is neurotoxicity. Several factors indicate that DFO causes neurotoxicity through the formation of oxygen free radical and by inhibiting the action of essential enzymes.\textsuperscript{30} However, their effects vary from individual to individual, which ought not to be ignored. Neurological anomalies primarily associated with this therapy are the loss of auditory and optic perception. However, these conditions are hard to diagnose due to its subclinical nature. Some of these anomalies are:

**DFO OTOXICITY:** DFO Therapy negatively intervenes and exacerbates the auditory pathway of thalassemic patients disrupting their sensory-neural response.\textsuperscript{22,49} Upon cessation, reverses this illness but leaving them with a minor discrepancy in their auditory perception.

**DFO INDUCED OPTIC NEUROPATHY:** Recent studies showed that loss of optic perception was associated with DFO toxicity among thalassemic patients.\textsuperscript{22,50} It was observed in Orton’s study that when chelation therapy was stopped, it resulted in a slight visual loss; however, one of the children experienced severe vision loss in one eye.\textsuperscript{51}

**DFO ASSOCIATED PERIPHERAL NEUROPATHY:** In contrast to other neurotoxicity, peripheral neuropathy may also be the result of DFO regime.\textsuperscript{19,20,34} Clinical manifestation of their condition is characterized by myalgias, attenuate muscle power, and paresthesia, which can be analyzed through neurophysiological tests.

**COGNITIVE DEFICITS**

Beta-thalassemia causes cognitive deficit and was first described by Orsini and their colleagues which was further confirmed by Monstero et al, by performing a different spectrum of neuropsychological tests.\textsuperscript{32,53} Their results showed that intellectual incapacitation was higher in those adults’ thalassemic patients who had hemosiderosis. While in thalassemic children who had mild cognitive dysfunction with an IQ less than 85 were seen in Economou et al, study.\textsuperscript{54} It was first assumed that hypoxia causes cognitive deficit due to insufficient blood supply to the brain. On the other hand, iron deposition in critical areas of the brain (which contributes towards proper cognitive functioning), also leads to intellectual impairment. A study performed by Metafratzi and their colleagues\textsuperscript{55} disclosed that putamen, caudate nucleus, and temporal and motor cortex are the sites where the high iron deposition was recorded which affects memory and proper cognitive functioning. Regular checkups, the specific time interval between blood transfusions and on time administration of deferroxamine and transfusions can alleviate the chances of intellectual incapacitation associated with beta thalassemia. Recent studies indicated that the intellectual ability of these patients does not change considerably as compared to non-affected individuals.\textsuperscript{56-57} However, in Duman’s study, their patients indicated significantly impaired cognitive skills and recognition of stimulus along with aberrant processing of information.\textsuperscript{56} So, this intellectual deficit and abnormal IQ could be the result of sub-clinical brain lesions or aberrant evoked potential.

Apart from beta thalassemia, thalassemia-intermedia patients’ intellect is also affected, which is prominent from the Teli’s study.\textsuperscript{54} They thoroughly evaluated the thalassemia-intermedia patients IQ by using the Weschler intelligence scale and found that out of 24 patients, approximately three patients had an IQ level less than 85, whereas two patients showed modest intellectual disability. High iron deposition in the patients or brain atrophy might be the triggering agent behind their intellectual discordance. However, according to Jokinen et al., cognitive decline is aggravated with cerebral atrophy.\textsuperscript{57} Thus, to prevent intellectual incapacitation, there is a strong need to diagnose this condition before onset, so the quality of life and disease management among these affected individuals can be improved. Psychometric scales allow doctors to evaluate the neuropsychology of an individual whereas in the case of beta-thalassemia patient’s literature regarding cognitive functioning among thalassemic patients is highly finite.

**POSSIBLE THERAPEUTIC INTERVENTION**

**HYDROXYCARBAMIDE:**

Hydroxycarbamide or hydroxyurea is a therapeutic molecule composed of hydroxylated urea previously used for sickle cell anemia but nowadays, utilized in beta-thalassemia.\textsuperscript{58} It has been observed that the administration of hydroxycarbamide (10–20 mg/kg per day) in these individuals promote gamma-globin expression and increases fetal hemoglobin level (HbF).\textsuperscript{59,60} This intervention remarkably improves various hematological anomalies (extramedullary hematopoeis and splenomegaly) that instigate neurological deficits in thalassemia affected individuals.
However, long term administration of hydroxyurea has shown some deleterious adverse effects in thalassemia patients', i.e. hematopoietic toxicity, hyperpigmentation, gastrointestinal issues along with disrupted liver enzymes levels that might give rise to other anomalies. Therefore, continuous follow up are required to monitor the effects, and also additional studies are required to optimize their regular dosage to minimize the adverse interaction among these beta-thalassemia patients.

DFO TOXICITY TREATMENT

Deferoxamine toxicity can be efficiently tackled by using hepcidin, a short peptide that could ameliorate iron overload by reducing the iron level in blood serum of these affected individuals. Hbb

mi mice studies indicated that low level of hepcidin causes more absorption of iron in the blood.

However, by the administration of a structured dose of hepcidin, regulates the iron concentration in the serum and also reduces damage caused to erythrocytes by ferric ions.

TREATMENT OF NEUROPATHIES

Neuropathy can be alleviated by using calcium channel α-2-γ subunits inhibitors as they interact with primary afferent nociceptors by binding to calcium channel, thereby inhibiting the release of the neurotransmitter. Gabapentin and Pregabalin widely employed drugs whose effects are studied in many neuropathic syndromes. However, they affect renal functioning. Therefore, it is advised that their dosage must be adjusted for a better therapeutic outcome in these patients.

GENE THERAPY

Gene therapy is a mainstream molecular technique through which a mutated gene can be substituted with therapeutic nucleic acid through viral vectors to revive the normal homeostasis impeded by mutated protein products. In the case of beta-thalassemia, BCL11α is a transcriptional factor that is encoded by the BCL11A gene whose function is to regulate fetal hemoglobin (HbF) to hemoglobin A (HbA) in adult red blood cells. It has been assumed that re-modulating fetal hemoglobin concentration can correct the beta-globulin chains of hemoglobin. Such a technique can be performed by procuring autologous cells, fixing the mutation, repopulation of recombinant stem cells to an optimum level, and reintroduction of stem cells in the affected individual. This approach not only revives the normal integrity of red blood cells but can also mitigate neurological anomalies aggravated with such genetic conditions. But this technique is currently facing various challenges such as controlling transgene expression, the safety of viral vectors, off-target insertion, and exaggerated immunological response. Once these challenges are rigorously dealt can effectively qualify for clinical studies and trials.

CONCLUSION

Up till now, there is no possible curative therapy available for this condition except for bone marrow transplant. However, there has been a substantial improvement in thalassemia therapeutics to ameliorate patients' survival and quality of life which includes suppressing the iron accumulation in visceral organs, fulfilling the circulatory demand, by averting the development of hematological malignancies, efficiently tackling neurotoxicity and neuropathy by employing iron regulators (hepcidin) and calcium channels inhibitors. Since these therapeutic interventions proposed for beta-thalassemia are either under clinical trials or performed at a small clinical setting, therefore, further research studies and large-scale clinical trials are needed to evaluate their efficacy in the amelioration of beta-thalassemia.

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