Ann Hematol (2015) 94:1261–1265
DOI 10.1007/s00277-015-2378-z

REVIEW ARTICLE

Neurological complications of beta-thalassemia

P. Nemtsas[1] · **M. Arnaoutoglou**[1] · **V. Perifanis**[2] · **E. Koutsouraki**[1] · **A. Orologas**[1]

Received: 15 September 2014 / Accepted: 8 April 2015 / Published online: 24 April 2015

Abstract The thalassemias are the most common single gene disorder in the world. Over the last years, several reports have demonstrated neurological complications in beta-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. Chronic hypoxia, iron overload, desferrioxamine neurotoxicity, and bone marrow expansion are implicated, but sufficient explanatory evidence is lacking and development of biomarkers is needed. This review summarizes current knowledge of the neurological complications. As life expectancy for beta-thalassemia patients increases, we support the use of neurophysiological, neuropsychological, or neuroimaging monitoring, enabling the evaluation of neural pathway impairment, to achieve appropriate management and as a result a better quality of life for this patient group.

Keywords Extramedullary hematopoiesis · Cerebrovascular disease · Peripheral neuropathy · Desferrioxamine neurotoxicity

✉ P. Nemtsas
pnemtsas@med.auth.gr

[1] First Department of Neurology, University General Hospital of Thessaloniki AHEPA, St.Kiriakidis 1, 546 36, Thessaloniki, Greece

[2] First Propedeutic Department of Internal Medicine, University General Hospital of Thessaloniki AHEPA, Thessaloniki, Greece

Introduction

Beta-thalassemia syndromes are a group of hereditary disorders characterized by a genetic deficiency in the synthesis of beta-globin chains. In the homozygous state, beta-thalassemia (i.e., thalassemia major, b-TM) causes severe, transfusion-dependent anemia. In the heterozygous state, the beta-thalassemia trait (i.e., thalassemia minor) causes mild to moderate microcytic anemia [1, 2]. The term "beta-thalassemia intermedia" refers to patients with symptomatic beta-thalassemia who do not require transfusion during at least the first few years of life and are able to survive into the second decade of life without chronic hypertransfusion therapy. While most patients with thalassemia intermedia do not need regular blood transfusions to survive, the effects of the disease, including bone marrow expansion, hepatosplenomegaly, and chronic hemolytic anemia, are present, even in milder forms of the disorder [3, 4]. The life expectancy of thalassemia patients has markedly improved over the last few decades, but patients still suffer from many complications of their congenital chronic disease, and several new complications are now being recognized, including neurological complications. This review highlights the most important neurological complications and the precautionary exams that are needed and provides guidelines for early treatment, where documented knowledge is available.

Neurological complications

Central and peripheral nervous system complications have been demonstrated in several reports. In most cases, these complications remained subclinical and were detected only during neurophysiological or neuroimaging evaluation. Chronic hypoxia, iron overload, desferrioxamine (DFO)

neurotoxicity, and bone marrow expansion are implicated as possible causes, but sufficient explanatory evidence and biomarker development are lacking. An increased understanding and improved biomarkers are critical because as survival rates improve, nervous system involvement is expected to become more conspicuous.

Intelligence quotient–cognitive function

Intellectual impairment in b-TM was first reported by Orsini et al. [5]. Later, Monastero et al. [6] performed a comprehensive neuropsychological battery including tests of abstract reasoning, attention, executive functions, language, and constructional and visuospatial skills, as well as memory and reported cognitive impairment in adult patients with b-TM, particularly in those patients presenting with hemosiderosis. Economou et al. [7] described mild mental retardation in three of 22 children with b-TM and abnormal total intelligence quotient (IQ) scores (<85) in 36.4 % of children with b-TM. Anemia, which leads to hypoxia, was the first factor correlated with intellectual impairment. Iron deposition, which leads to brain damage in the long term, is another important factor that has been linked to developing central nervous system (CNS) complications in b-TM patients. Metafratzi et al. [8] reported higher iron depositions in the putamen, caudate nucleus, and motor and temporal cortex of patients with b-TM. These areas are important for cognitive function as well as for implicit and explicit memory. Better monitoring, increased time interval between the transfusions, earlier onset of blood transfusions, and earlier onset of DFO therapy can all reduce impairment. Recently, Karimi and Duman [9, 10] reported that the IQ of b-TM patients does not differ significantly from the normal population. However, in Duman's study, cognitive impairment and impaired stimulus recognition and information processing were more frequently noted in the patient group. The discordance in the IQ results can be attributed to the exclusion from the study of patients with abnormal evoked related potentials (ERPs). Intellectual impairment has also been described in thalassemia intermedia patients. In Teli's study [11], patients with thalassemia intermedia were tested using Wechsler intelligence scales for children. The evaluation revealed a normal mean IQ, but 11.7 % had an IQ below 85 and 5.88 % had mild mental deficiency. Cognitive impairment in thalassemia intermedia could be attributed either to high iron deposition [12] or to the high percentage of cerebral atrophy (37 % of splenectomized patients) according to Taher et al. [13]. It is indeed well documented from the LADIS study that brain atrophy accelerates cognitive decline [14]. In conclusion, it is suggested that regular neuropsychological testing is essential for early diagnosis and appropriate management of cognitive dysfunction to improve the quality of life of patients with thalassemias.

Evoked potentials (VEPs, BAEPs, SSEPs)

Evoked potentials constitute a noninvasive method of evaluating the CNS. Evoked potentials lack disease specificity but remain sensitive tools in detecting even subclinical CNS lesions. Gelmi et al. [15] reported that visual evoked potential (VEP) abnormalities in b-TM patients correlated with iron overload. Pathological VEPs findings that were partially reversible were attributed to DFO neurotoxicity in several studies [7, 16, 17]. With regard to brainstem auditory evoked potentials (BAEPs), Wong [18] reported five (15 %) of the patients in his study with mild sensorineural loss and Triantafyllou [17] found that 14 out of 120 patients presented abnormal BAEP findings, mostly reversible and related to DFO neurotoxicity. The use of deferasirox [19] or deferiprone [20] in the management of iron overload has not been implicated in causing such abnormalities, but a limited number of studies exist. Wong [18] evaluated somatosensory evoked potentials (SSEPs) and described that 12 % of the patients in his study had increased cortical latencies of median or posterior tibial somatosensory evoked potentials. Pathological evoked potentials have also been described in thalassemia intermedia. Recently, Teli et al. [11] in an extensive study found that four out of 24 (16 %) patients with thalassemia intermedia presented with pathological BAEPs. Additionally, 4 % of the patients in their study revealed abnormal findings on SSEPs and all patients had normal VEPs. Because the majority of the latter patient group were nontransfused and under no iron chelation treatment, hypoxia and coagulopathy may be responsible for such lesions. The aforementioned results indicate that central nervous system lesions are not rare in either b-TM patients or in thalassemia intermedia, even if they remain subclinical and can be detected only by a careful assessment with specialized exams.

Extramedullary hematopoiesis and neurological complications

Extramedullary hematopoiesis (EMH) is a physiological compensatory phenomenon caused by insufficient bone marrow function that becomes unable to meet circulatory demands. EMH is seen in many hematological diseases; however, it commonly occurs in chronic anemias. The formation of extramedullary hematopoietic foci is slow and initially subclinical. Skull changes consist of the widening of diploid spaces and displacement and thinning of the outer surface and may lead to brain compression by the mass effect of the lesion. Since the first case described by Gatto et al. [21] in 1954, a large number of cases have been cited in the literature. Most frequently reported are cases concerning a paraspinal location of the hematopoietic tissue. The spectrum of the various clinical presentations that have been reported includes back pain, lower extremity pain, paresthesia, abnormal

proprioception, exaggerated or brisk deep tendon reflexes, Babinski response, Lasegue sign, paraparesis, paraplegia, ankle clonus, spastic gait, urgency of urination, and bowel incontinence. The size and location of lesions and the extent of spinal cord involvement determine the severity, acuteness, and multiplicity of signs and symptoms [22, 23]. In thalassemia intermedia, the occurrence of extramedullary hematopoiesis is even higher and rare complications have been reported. Particularly, narrowing of the optical canal with subsequent optic neuropathy and visual failure has been described [24, 25]. Meara [26] reported extramedullary hematopoiesis of the middle ear in a patient with thalassemia intermedia resulting in conductive hearing loss. Treatment options are transfusion therapy, irradiation of the masses, and synovectomy. Recently, induction of fetal hemoglobin with hydroxycarbamide has also been proposed as an efficient first-line treatment option for patients with EMH [27]. Early diagnosis of EMH will affect the course of management and may reduce the incidence of irreversible neurological damage that would otherwise occur with prolonged undiagnosed cord compression.

Cerebrovascular disease

The literature presents an increasing number of studies concerning hemoglobinopathies and cerebrovascular disease. In 1972, Logothetis et al. described a "stroke syndrome" compatible with transient ischemic attacks in about 20 % of 138 cases of b-TM in Greece [28]. Transient ischemic attacks presenting with headache, seizures, and hemiparesis were also found in 2.2 % of patients with b-TM by Borgna Pignatti et al. [29]. Most recent studies usually involve thromboembolic events in a mixed patient population with thalassemia major and thalassemia intermedia, with percentages ranging between 0.9–4 % and 3.9–29 %, respectively [18, 30–34]. Patients with b-TM seem to suffer mainly from large hemispheric territorial infarcts [35–37]. Cardioembolism due to siderotoxic cardiomyopathy and arrhythmias is assumed as one important etiology of stroke in b-TM [38]. Hemosiderosis-related disease, including cardiomyopathy, liver dysfunction, and diabetes mellitus [39], can be prevented by proper chelation therapy, and this therapy is also important in prevention of cerebrovascular accidents. Chronic anemia may lead to cerebral injury in patients who already have multiple risk factors for stroke [40]. The close monitoring and proper adjustment of hemoglobin levels that is prerequisite for thalassemia patients may prevent cerebral events due to hypoxia. However, because Metarugcheep et al. [41] and Taher et al. [13] were not able to correlate anemia as a contributing factor for brain lesions, caution is suggested in intensive transfusions, especially when giving large and rapid transfusions to thalassemic patients [42]. Cerebrovascular disease in beta-thalassemia intermedia patients usually presents with asymptomatic ischemic lesions that are smaller and affect deeper structures while sparing the cortex [32, 43, 44]. According to the OPTIMAL CARE study [45], thromboembolic disease, mostly venous, was the fifth most common complication, affecting 14 % of the patient population. The majority of thalassemia intermedia patients with silent cerebral infarcts were splenectomized [33, 34]. Taking into account the additional complications of splenectomy, reconsidering the latter as a procedure of choice (e.g., to improve anemia), and restricting it to cases of severe splenomegaly or hypersplenism leading to profound anemia or thrombocytopenia should be considered [33, 46]. Iron chelation therapy in transfusion-independent patients should also be considered, especially in the light of studies that associate abnormal brain magnetic resonance angiography and positron-emission tomography–computed tomography findings with iron overload parameters in patients with thalassemia intermedia [47–49]. Finally, a hypercoagulable state is one of the most notable risk factors associated with thrombotic stroke in beta-thalassemia major, as well as in thalassemia intermedia patients [11, 30, 31, 33, 34, 50–54]. The underlying mechanism of hypercoagulability primarily involves a dual role of activated platelets and hemolyzed red blood cells with thrombin generation potential. Other associated factors involve endothelial activation and disturbances in the coagulation system, collectively leading to a prothrombotic state [46]. Hence, diagnostic magnetic resonance imaging (MRI) is recommended in high-risk groups (patients of advanced age, splenectomy, transfusion independence, and iron toxicity) [34, 43], to screen for early asymptomatic brain damage. In cases where a recent infarction is suspected, diffusion-weighted MRI (DW-MRI) is the method of choice to detect it [34, 55]. Interestingly, in a recent study, hydroxycarbamide administration was associated with a lower incidence of white matter lesions in untransfused patients [55]. If brain ischemia is found, the administration of antiplatelet aggregants or blood transfusion is likely to be beneficial. In addition, in thalassemia patients with the complication of a thromboembolic event, secondary prophylaxis could be helpful in preventing cerebral thromboembolic events [33]. At this point, it is important to mention that caution is warranted because, although rare, cerebral hemorrhage has also been described, usually presenting with headache, hypertension, and convulsions and following the post transfusion period [56–58].

Peripheral neuropathy and myopathy

The literature concerning nerve conduction velocity (NCV) studies in thalassemic patients remains limited. Logothetis et al. [28] first described a myopathic syndrome in b-TM patients with proximal weakness, mainly in the lower limbs, accompanied by a myopathic electromyographic pattern. However, patients in their study were children and were

treated quite differently than current patients. Papanastasiou et al. [59] reported that 22 % of the patients in their study developed a mild peripheral neuropathy, mainly motor, during the second decade of life. In contrast, Zafeiriou et al. [60] reported that 10 % of patients had clinical evidence of a sensory neuropathy (absent or diminished deep tendon reflexes and loss of sensation in a stock-glove distribution) and additionally 25 % had decreased sensory conduction velocities, and only 10 % also had decreased motor NCVs. A mainly sensory polyneuropathy in 53 to 78 % of patients has been also described in more recent studies [61, 62]. Thalassemia intermedia patients also suffer from a mild motor peripheral neuropathy according to Papanastasiou et al. [59]. In the latter study, no difference in the frequency of peripheral neuropathy among the patients with thalassemia intermedia and thalassemia major was observed. Interestingly, differences in the neurophysiological findings between the different thalassemia types were found in a study by Sawaya et al. The neuropathy was mainly sensory and seemed to be worse in the intermedia type. Thalassemic patients who received blood transfusions and deferoxamine had a better nerve function than those who did not, irrespective of the dose of deferoxamine. The neuropathy was worse for older patients, irrespective of sex [62]. Peripheral neuropathy is a reality that reduces daily activities and hampers the quality of life of a high proportion of thalassemic patients. It has been attributed to multiple factors, but a sufficient illustration of the causative reasons is limited. Precautionary neurophysiological monitoring to achieve the appropriate management has been proposed [63].

Conclusion

As life expectancy for beta-thalassemia patients increases, several new neurological complications are now being recognized. Early detection of these initially subclinical complications with the use of neurophysiological, neuropsychological, or neuroimaging monitoring becomes imperative, enabling the evaluation of neural pathway impairment. The clarification of the pathophysiological mechanisms underlying these complications and development of biomarkers will facilitate the appropriate management needed to achieve a better quality of life for this patient group.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Rund D, Rachmilewitz E (2005) Beta-thalassemia. N Engl J Med 353:1135–1146
2. Cao A, Galanello R (2010) Beta-thalassemia. Genet Med 12:61–76
3. Aessopos A, Farmakis D, Karagiorga M et al (2001) Cardiac involvement in thalassemia intermedia: a multicenter study. Blood 97:3411–3416
4. Taher AT, Musallam KM, El-Beshlawy A et al (2010) Age-related complications in treatment-naive patients with thalassaemia intermedia. Br J Haematol 150:486–489
5. Orsini A, Soulayrol R, Tramini F, Tasso-Perrimond AM (1967) Nervous manifestations associated with thalassemia (critical study of the concept of thalassemic neurohemolytic syndrome). Pediatrie 22:771–784
6. Monastero R, Monastero G, Ciaccio C et al (2000) Cognitive deficits in beta-thalassemia major. Acta Neurol Scand 102:162–168
7. Economou M, Zafeiriou DI, Kontopoulos E et al (2006) Neurophysiologic and intellectual evaluation of beta-thalassemia patients. Brain Dev 28:14–18
8. Metafratzi Z, Argyropoulou MI, Kiortsis DN et al (2001) T(2) relaxation rate of basal ganglia and cortex in patients with beta-thalassaemia major. Br J Radiol 74:407–410
9. Karimi M, Yarmohammadi H, Cappellini MD (2006) Analysis of intelligence quotient in patients with homozygous beta-thalassemia. Saudi Med J 27:982–985
10. Duman O, Arayici S, Fettahoglu C et al (2011) Neurocognitive function in patients with beta-thalassemia major. Pediatr Int 53: 519–523
11. Teli A, Economou M, Rudolf J et al (2012) Subclinical central nervous system involvement and thrombophilic status in young thalassemia intermedia patients of Greek origin. Blood Coagul Fibrinolysis 23:195–202
12. Tony S, Daar S, Elshinawy M et al (2012) T2* MRI in regularly transfused children with thalassemia intermedia: serum ferritin does not reflect liver iron stores. Pediatr Hematol Oncol 29:579–584
13. Taher AT, Musallam KM, Nasreddine W et al (2010) Asymptomatic brain magnetic resonance imaging abnormalities in splenectomized adults with thalassemia intermedia. J Thromb Haemost 8:54–59
14. Jokinen H, Lipsanen J, Schmidt R et al (2012) Brain atrophy accelerates cognitive decline in cerebral small vessel disease: the LADIS study. Neurology 78:1785–1792
15. Gelmi C, Borgna-Pignatti C, Franchin S et al (1988) Electroretinographic and visual-evoked potential abnormalities in patients with beta-thalassemia major. Ophthalmologica 196:29–34
16. Marciani MG, Cianciulli P, Stefani N et al (1991) Toxic effects of high-dose deferoxamine treatment in patients with iron overload: an electrophysiological study of cerebral and visual function. Haematologica 76:131–134
17. Triantafyllou N, Fisfis M, Sideris G et al (1991) Neurophysiological and neuro-otological study of homozygous beta-thalassemia under long-term desferrioxamine (DFO) treatment. Acta Neurol Scand 83:306–308
18. Wong V, Li A, Lee AC (1993) Neurophysiologic study of beta-thalassemia patients. J Child Neurol 8:330–335
19. Taher A, Cappellini MD (2009) Update on the use of deferasirox in the management of iron overload. Ther Clin Risk Manag 5: 857–868
20. Tourkantoni N, Athanassiou-Metaxa M, Zafiriou D et al (2008) Immune and neural status of thalassemic patients receiving deferiprone or combined deferiprone and deferoxamine chelation treatment. Hemoglobin 32:35–40
21. Gatto I, Terrana V, Biondi L (1954) Compression of the spinal cord due to proliferation of bone marrow in epidural space in a splenectomized person with Cooley's disease. Haematologica 38: 61–76
22. Haidar R, Mhaidli H, Taher AT (2010) Paraspinal extramedullary hematopoiesis in patients with thalassemia intermedia. Eur Spine J 19:871–878

23. Orphanidou-Vlachou E, Tziakouri-Shiakalli C, Georgiades CS (2014) Extramedullary hemopoiesis. Semin Ultrasound CT MR 35:255–262
24. Aarabi B, Haghshenas M, Rakeii V (1998) Visual failure caused by suprasellar extramedullary hematopoiesis in beta thalassemia: case report. Neurosurgery 42:922–925, discussion 925–926
25. Sorcinelli R, Cacace E, Del Piano M (1999) Optic nerve compression by extramedullary hematopoietic tissue in a patient suffering from beta-thalassemia intermedia. Metab Pediatr Syst Ophthalmol 22–23:5–6
26. Meara JG, Potter C, Goodman M, Vernick D (1998) Extramedullary hematopoiesis of the middle ear in a patient with thalassemia. Am J Otolaryngol 19:287–289
27. Karimi M, Cohan N, Pishdad P (2014) Hydroxyurea as a first-line treatment of extramedullary hematopoiesis in patients with beta thalassemia: four case reports. Hematology
28. Logothetis J, Constantoulakis M, Economidou J et al (1972) Thalassemia major (homozygous beta-thalassemia). A survey of 138 cases with emphasis on neurologic and muscular aspects. Neurology 22:294–304
29. Borgna Pignatti C, Carnelli V, Caruso V et al (1998) Thromboembolic events in beta thalassemia major: an Italian multicenter study. Acta Haematol 99:76–79
30. Cappellini MD, Robbiolo L, Bottasso BM et al (2000) Venous thromboembolism and hypercoagulability in splenectomized patients with thalassaemia intermedia. Br J Haematol 111:467–473
31. Eldor A, Durst R, Hy-Am E et al (1999) A chronic hypercoagulable state in patients with beta-thalassaemia major is already present in childhood. Br J Haematol 107:739–746
32. Michaeli J, Mittelman M, Grisaru D, Rachmilewitz EA (1992) Thromboembolic complications in beta thalassemia major. Acta Haematol 87:71–74
33. Haghpanah S, Karimi M (2012) Cerebral thrombosis in patients with beta-thalassemia: a systematic review. Blood Coagul Fibrinolysis 23:212–217
34. Cappellini MD, Poggiali E, Taher AT, Musallam KM (2012) Hypercoagulability in beta-thalassemia: a status quo. Expert Rev Hematol 5:505–511, quiz 512
35. Zafeiriou DI, Prengler M, Gombakis N et al (2004) Central nervous system abnormalities in asymptomatic young patients with Sbeta-thalassemia. Ann Neurol 55:835–839
36. Karimi M, Khanlari M, Rachmilewitz EA (2008) Cerebrovascular accident in beta-thalassemia major (beta-TM) and beta-thalassemia intermedia (beta-TI). Am J Hematol 83:77–79
37. Taher A, Isma'eel H, Mehio G et al (2006) Prevalence of thromboembolic events among 8,860 patients with thalassaemia major and intermedia in the Mediterranean area and Iran. Thromb Haemost 96:488–491
38. Vassilopoulou S, Anagnostou E, Paraskevas G, Spengos K (2011) Etiology and treatment of ischaemic stroke in patients with beta-thalassemia major. Eur J Neurol 18:1426–1428
39. Mavrogeni S, Bratis K, van Wijk K et al (2013) The reproducibility of cardiac and liver T2* measurement in thalassemia major using two different software packages. Int J Cardiovasc Imaging
40. McClellan W, Warnock DG, McClure L et al (2006) Racial differences in the prevalence of chronic kidney disease among participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Cohort Study. J Am Soc Nephrol 17: 1710–1715
41. Metarugcheep P, Chanyawattiwongs S, Srisubat K, Pootrakul P (2008) Clinical silent cerebral infarct (SCI) in patients with thalassemia diseases assessed by magnetic resonance imaging (MRI). J Med Assoc Thai 91:889–894
42. Paolino E, Monetti VC, Granieri E, Boldrini P (1983) Acute cerebrovascular insults in homozygous beta-thalassaemia: a case report. J Neurol 230:37–41
43. Karimi M, Bagheri H, Rastgu F, Rachmilewitz EA (2010) Magnetic resonance imaging to determine the incidence of brain ischaemia in patients with beta-thalassaemia intermedia. Thromb Haemost 103: 989–993
44. Musallam KM, Taher AT, Karimi M, Rachmilewitz EA (2012) Cerebral infarction in beta-thalassemia intermedia: breaking the silence. Thromb Res 130:695–702
45. Taher AT, Musallam KM, Karimi M et al (2010) Overview on practices in thalassemia intermedia management aiming for lowering complication rates across a region of endemicity: the OPTIMAL CARE study. Blood 115:1886–1892
46. Taher AT, Musallam KM, Cappellini MD, Weatherall DJ (2011) Optimal management of beta thalassaemia intermedia. Br J Haematol 152:512–523
47. Musallam KM, Beydoun A, Hourani R et al (2011) Brain magnetic resonance angiography in splenectomized adults with beta-thalassemia intermedia. Eur J Haematol 87:539–546
48. Musallam KM, Nasreddine W, Beydoun A et al (2012) Brain positron emission tomography in splenectomized adults with beta-thalassemia intermedia: uncovering yet another covert abnormality. Ann Hematol 91:235–241
49. Taher AT, Musallam KM, Viprakasit V et al (2014) Iron chelation therapy for non-transfusion-dependent thalassemia (NTDT): a status quo. Blood Cells Mol Dis 52:88–90
50. Bhattacharyya M, Kannan M, Chaudhry VP et al (2007) Hypercoagulable state in five thalassemia intermedia patients. Clin Appl Thromb Hemost 13:422–427
51. Cappellini MD, Motta I, Musallam KM, Taher AT (2010) Redefining thalassemia as a hypercoagulable state. Ann N Y Acad Sci 1202:231–236
52. Eldor A, Rachmilewitz EA (2002) The hypercoagulable state in thalassemia. Blood 99:36–43
53. Sirachainan N (2013) Thalassemia and the hypercoagulable state. Thromb Res 132:637–641
54. Taher AT, Musallam KM, Inati A (2009) The hypercoagulable state in thalassemia intermedia. Hemoglobin 33(Suppl 1):S160–169
55. Karimi M, Haghpanah S, Bagheri MH et al (2012) Frequency and distribution of asymptomatic brain lesions in patients with beta-thalassemia intermedia. Ann Hematol 91:1833–1838
56. Wasi P, Na-Nakorn S, Pootrakul P et al (1978) A syndrome of hypertension, convulsion, and cerebral haemorrhage in thalassaemic patients after multiple blood-transfusions. Lancet 2: 602–604
57. Constantopoulos A, Matsaniotis N (1980) Hypertension, convulsion, and cerebral haemorrhage in thalassaemic patients after multiple blood transfusions. Helv Paediatr Acta 35: 269–271
58. Masood SA, Zaidi A (2012) Post-transfusion hypertension, convulsion and intracranial haemorrhage in beta-thalassemia major. J Coll Physicians Surg Pak 22:473–475
59. Papanastasiou DA, Papanicolaou D, Magiakou AM et al (1991) Peripheral neuropathy in patients with beta-thalassaemia. J Neurol Neurosurg Psychiatry 54:997–1000
60. Zafeiriou DI, Kousi AA, Tsantali CT et al (1998) Neurophysiologic evaluation of long-term desferrioxamine therapy in beta-thalassemia patients. Pediatr Neurol 18:420–424
61. Stamboulis E, Vlachou N, Drossou-Servou M et al (2004) Axonal sensorimotor neuropathy in patients with beta-thalassaemia. J Neurol Neurosurg Psychiatry 75:1483–1486
62. Sawaya RA, Zahed L, Taher A (2006) Peripheral neuropathy in thalassaemia. Ann Saudi Med 26:358–363
63. Nemtsas P, Perifanis V, Koutsouraki E, Orologas A, Arnaoutoglou M (2014) P627: is precautionary neurophysiological monitoring useful for beta-thalassemia patients? Clin Neurophysiol 125(Suppl 1):S219