


Headache: an important symptom possibly linked to white matter lesions in thalassaemia

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The major forms of the β -thalassaemias are among the most common monogenic disorders worldwide (Weatherall, 2010; Taher *et al*, 2018). They span a broad clinical spectrum, from the phenotypically more severe thalassaemia “major” (TM) or transfusion-dependent thalassaemia (TDT), which is generally associated with a requirement for monthly blood transfusions from infancy (Weatherall, 2010), to diverse milder phenotypes classically termed thalassaemia “intermedia” (TI) (Thein, 2005) or, more recently, “non-transfusion-dependent” thalassaemia (NTDT) (Taher *et al*, 2011). Identified within both phenotypes are patients with the most common form of β -thalassaemia worldwide, Haemoglobin (Hb) E thalassaemia (EBT) resulting from the inheritance of a thalassaemia allele and the β chain variant HbE; some affected patients with EBT are transfusion-dependent from infancy, while others require virtually no transfusion support lifelong (Olivieri, 2012).

Summary

Neurological manifestations are reported only occasionally in patients with thalassaemia and are given much less prominence than the complications related to anaemia and iron overload. White matter changes (WMCs) on magnetic resonance imaging (MRI) in patients with thalassaemia were first reported two decades ago but the significance of these lesions remains unclear. We studied the neurological and cognitive manifestations in 82 older patients with thalassaemia [25 Thalassaemia major (TM), 24 thalassaemia intermedia (TI) and 33 haemoglobin E β thalassaemia (EBT)] and 80 controls, and found that headaches were more common in thalassaemia patients (50/82, 61%) than in controls (18/80, 22.5%: $P < 0.001$). WMCs on MRI were found in 20/82 (24.3%) patients and 2/29 (6.9%) controls had ($P = 0.078$). WMC were more common among those with headaches (17/50: 34%) than in those without headache (3/32; 9.3%) ($P = 0.023$). WMCs were not associated with reduction of cognition. Nevertheless, cognition was lower in the TI and EBT groups compared with those with TM ($P = 0.002$). The association of headache with WMC in thalassaemia has not been reported before and warrants further study.

Keywords: β -thalassaemia, stroke, headache, white matter lesions.

The β -thalassaemias are the most common inherited diseases in Sri Lanka. The numbers affected with TM, EBT of variable severity, and TI (which is genetically distinct from that in the Middle East and Mediterranean), have roughly doubled over the last 20 years, imposing an increasingly significant health burden on the country’s healthcare delivery systems (De Silva *et al*, 2000; Premawardhena *et al*, 2005; Perera *et al*, 2015).

Once regarded as a more favourable diagnosis, TI has been reported to be associated with various morbidities in adulthood (Eldor & Rachmilewitz, 2002; Cappellini *et al*, 2010; Taher *et al*, 2010a,b; Musallam *et al*, 2012a, 2013).

Neurological changes have been described only infrequently in patients with thalassaemia. Davison and Wechsler (1939) reported a patient with TM who developed extrapyramidal features “similar to that of Wilson’s disease”. Convulsions (Portier *et al*, 1952; Cruz Hernandez & Valesco,

1961; Logothetis *et al*, 1972) associated with hypertension and cerebral haemorrhage following blood transfusion, and cerebral infarctions developing in patients with TM and TI have all been reported in case reports or case series (Sinniah *et al*, 1977; Wasi *et al*, 1978; Constantopoulos & Matsaniotis, 1980). Abnormal electroencephalogram (EEG) findings were reported in 33–70% of thalassaemia patients (Amabile *et al*, 1987; Teli *et al*, 2012); they were purported to reflect hypoxia-induced cortical abnormalities (Amabile *et al*, 1987), but neurological symptoms were not reported in parallel with such changes. Reductions in cognitive function have been reported in both TM and TI (Monastero *et al*, 2000; Koutelkos & Haliasos, 2013), but no differences were identified between TI and TM (Elhabiby *et al*, 2016).

Nearly 20 years ago, WMCs (also termed white matter lesions/WMLs) on MRI, in the absence of clinical neurological manifestations were first reported in a group of patients with TI (Manfrè *et al*, 1999). These so-termed “silent” cerebral infarctions (SCIs), possibly reflecting the presence of small-vessel disease (Weber & Knopf, 2006; Vernooij *et al*, 2007; LADIS group, 2011), are considered to be more frequent in patients with TI than with TM (Cappellini *et al*, 2000; Taher *et al*, 2006; Mannucci, 2010; Musallam *et al*, 2012a,b). A recent study however showed that the incidence of these lesions is as high as 60% in adults with β TM (Pazgal *et al*, 2016). The only available study on EBT reported the presence of WMCs in 24% of the subjects studied. (Metarugcheep *et al*, 2008). WMCs, although relatively recently described in thalassaemic patients, have long been known to occur in patients with sickle cell disease (SCD) (Miller *et al*, 2001; LADIS group, 2011; Debaun *et al*, 2012). They are well recognised in older people without any haemoglobin disorders, in whom the primary risk factors for development of WMCs are thought to be advanced age and hypertension (Vernooij *et al*, 2007; LADIS group, 2011). Their occurrence is clearly linked to age as they are described in only about 2% of healthy young men aged 20 years (Weber & Knopf, 2006) compared to 20–35% in those over the age of 65 years. (Brant-Zawadzki *et al*, 1985) WMCs are clearly emerging as an important factor influencing cognitive performance, as well as progression of disabilities (Pantoni *et al*, 2007; LADIS group, 2011). In patients with SCD, for example, SCIs are associated with declines in intellectual ability, poor academic achievement and risk of stroke (Armstrong *et al*, 1996; Bernaudin *et al*, 2000; Brown *et al*, 2000; Miller *et al*, 2001; Debaun *et al*, 2012).

In contrast, the clinical relevance of SCIs is less clear in patients with thalassaemia (Taher *et al*, 2006; Metarugcheep *et al*, 2008; Musallam *et al*, 2011, 2012b). Abnormal findings so far identified by MRI, EEG or neurocognitive testing in thalassaemia have been generally clinically silent (Teli *et al*, 2012).

Neurological symptoms have been only infrequently described in thalassaemia, and there have been only a few publications on headache. Most of the reports on headache were of patients with TM or TI who have developed vascular

events, including cerebral venous thrombo-embolism or Moya Moya disease (Ho *et al*, 2006; Eskazan *et al*, 2011; Akpınar *et al*, 2015).

In contrast, headache is well described in patients with SCD, including in those with SS, SC, $S\beta^0$ -thalassaemia, and $S\beta^+$ -thalassaemia. A review of neurological complications of SCD in Africa found the prevalence of recurrent headache in five pooled studies to be 18.9%. (Noubiap *et al*, 2017). The symptom of headache in SCD in all genotypes is probably multifactorial and may be related to migraine, vaso-occlusive events, bone marrow hyperplasia, obstructive sleep apnoea or cerebral vessel stenosis. In a case-control study of children with SCD, the frequency of headache was not different between those with SCD and normal controls (Niebank *et al*, 2007). Although MRI changes were common in SCD patients in the above study, the authors were unable to show any association of headache with MRI changes or an association with the presence of strokes in these children.

An estimated 2000–3000 patients with severe β -thalassaemia (TM, EBT and β TI) attend transfusion centres in Sri Lanka. The risks of neurological disease in these patients remain poorly defined.

This study aimed to describe the clinical, neuro-radiological, neuro- electrophysiological and cognitive dysfunction in older patients with different types of thalassaemia and compare them with an age- and gender-matched non-thalassaemic cohort.

Materials and methods

The study was conducted in adults with thalassaemia, both regularly and irregularly transfused, managed at the Adolescent and Adult Thalassaemia Care Unit, North Colombo (Teaching) Hospital, Ragama, Sri Lanka between June 2014 and June 2016. Details of transfusion history, laboratory results and additional clinical data were obtained from clinic notes. An age- and sex-matched non-thalassaemic control group was recruited from the employees of the North Colombo (teaching) Hospital personnel, including hospital orderlies, nursing students, nurses and technical officers. Sixteen of the controls were relatives of thalassaemia patients whilst the other 64 were unrelated. Ethical approval was obtained from the Ethical Review Committee of the Faculty of Medicine University of Kelaniya (P/183/09/2014). Informed written consent was obtained from each participant.

Neurological assessment

A single consultant neurologist performed detailed neurological evaluations, which consisted of a history of neurological symptoms, including that of chronic headache, syncope and seizures, and a complete neurological examination in the thalassaemia cases; while only the headache and neurocognitive evaluation was carried out in the control group. Headache was classified using the International Classification of

Headache Disorders -3 guidelines (ICHD-3; Headache Classification Committee of the International Headache Society (IHS), 2013).

Brain MRI and intracranial magnetic resonance angiography (MRA) were obtained with a 1.5-T scanner (SIGNA HDXT system, GE Health Care, Waukesha, WI, USA) with an eight-channel head coil according to standard methods, by two trained MRI technicians. The MRI protocol was identical for all participants and included diffusion-weighted axial scans in 5 mm thickness, high resolution three-dimensional T1-weighted BRAVO sequences in 2 mm thickness, a three-dimensional T2-weighted sequence in 1.6 mm thickness, a three-dimensional fluid-attenuated inversion recovery (FLAIR) sequence in 1.6 mm thickness and three-dimensional Time of Flight (TOF) angio sequence. Intravenous contrast material was not administered. Transcranial Doppler was obtained in all patients with MRI abnormalities. A single consultant radiologist performed all the radiological evaluations.

WMCs were classified according to size [small (≤ 5 mm) or large (> 5 mm)] and anatomical distribution.

Cognitive function assessment

A detailed assessment of cognitive function was performed by a single consultant psychiatrist using the modified Montreal Cognitive function scale - Sinhala version (MOCA - S), a 30-point assessment scale used to evaluate several cognitive domains; a score of 24 or lower suggested cognitive dysfunction (Nasreddine *et al*, 2005; Karunaratne *et al*, 2011).

Trained medical research assistants collected data and statistical analysis was conducted using SPSS version 24 (IBM SPSS Statistics for Windows, Version 24.0. IBM Corp. Armonk, NY.).

Results

We studied 82 patients [thalassaemia major ($n = 25$), irregularly transfused patients with thalassaemia intermedia ($n = 24$) and HbE- β thalassaemia ($n = 33$)] and 80 controls. Table I lists the main characteristics of the three patient groups. Half of the patients ($n = 41$) were male, and the mean age (\pm standard deviation, SD) was 32 ± 18 (range 10–62) years. Two patients with TM patients were below the age of 20 years, which was initially designated as the minimal age of recruitment. They were considered for analysis nevertheless. The 80 controls (51.25% males) were aged 33 ± 10 (range 20–65) years. Neurological evaluation, including MRI/MRA, was done in all patients and controls with headache. MOCA cognitive assessment was performed in 77 patients and 79 controls; it was not performed in two patients with TM, two with TI and one with EBT due to associated severe depression or language non-comprehension.

Transfusion history was distinct in the three groups of patients. Over the preceding 12 months, patients with TM had received at least 8 transfusions and TI patients had less than 8

transfusions - although most had far fewer than 8 transfusions. The group with EBT had more complex transfusion histories: while most were presently infrequently transfused (only 2/33 had received > 8 transfusions in 2015; only 9/33 had received > 8 transfusions in 2016), 20 (61%) had received ≥ 50 transfusions lifelong. In this more heavily transfused group, the mean number of transfusions was 133 ± 9 (50–400); the other 13 patients (49%) had been less intensively transfused, having received 23 ± 23 (0–48) transfusions lifelong.

Twelve patients (three patients with TM, four with TI and five with EBT) had diabetes mellitus and none had hypertension. Eight reported a history of smoking whilst only four of them continued to smoke. Five controls had diabetes; one was hypertensive and 10 reported a history of smoking.

Neurological evaluation

A history of seizures was present in six patients, three with TM and three with EBT; one of the controls had seizures. In two patients, the onset of seizures had followed meningoen- cephalitis.

A striking finding was a much higher frequency of recurrent headaches in patients with thalassaemia compared to controls. A total of 50/82 (61%; 95% confidence interval 50–71%) patients with thalassaemia complained of recurrent headaches, compared to 18 of 80 (22.5%) controls ($P < 0.001$). This included 12 (48%) patients with TM, 14 (58.3%) with TI and 24 (72.3%) with EBT. There was no statistically significant difference in the frequency of headaches between the three different phenotypes of thalassaemia ($P = 0.153$), or when comparing TM patients with the two less intensively transfused phenotypes, considered as one group (TI and EBT) ($P = 0.177$). The main headaches reported were migraine without aura (17, 34%), migraine with aura (13, 26%), tension type headache (8, 16%), and headaches attributed to disorder of haemostasis (10, 20%); the remaining headaches were miscellaneous in description.

Among the 18 controls that reported headache, 14 (82.3%) had migraines (4 with aura, 10 without aura), three were diagnosed with rhinosinusitis and one had a tension type headache.

MRI and MRA changes

White matter changes (WMCs) on MRI were identified in 20 (24.3%) of 82 patients and 2 (6.9%) of 29 controls ($P = 0.078$). A brain MRI scan was done in 29 of the 80 controls, including all 18 controls with headache. WMCs were identified in 5 (20%) patients with TM, 7 (29.2%) patients with TI and 8 (24.2%) patients with EBT; these prevalences were not significantly different between groups ($P = 0.756$). None of the patients with WMCs had diabetes mellitus or hypertension; two were smokers. The two control subjects with WMCs were both non-smokers with no history of hypertension and diabetes mellitus.

Table I. The main haematological and clinical characteristics of the three main categories of thalassaemia patients.

	β-thalassaemia major (<i>n</i> = 25)		HbE β-thalassaemia (<i>n</i> = 33)		β-thalassaemia intermedia (<i>n</i> = 24)	
	Mean	SD	Mean	SD	Mean	SD
Age at diagnosis	6.6 months	2.4	11.1 years	12.2	21.2 years	19.0
Age (years)	26	5	34	7	36	15
Total number of transfusions (<i>n</i>)	380	119	90.3	83.0	77.0	102
Mean ferritin (μg/l)	2310	1623	1171	912	1008	717
Mean platelet count ($\times 10^9/l$)	312	196	541	302	324	295
Mean Hb (g/l)	81	9.0	67	10	76	10
Splenectomised (%)	12 (48%)		24(72.72%)		9(37.5%)	

The main haematological and clinical characteristics of the three main categories of thalassaemia patients are summarized here. The patients with thalassaemia major were younger than the other two groups. They had presented at a younger age, had more blood transfusions, had higher mean haemoglobin (Hb) concentrations and also had higher serum ferritin values. The HbE β-thalassaemia group had the highest splenectomy rate and the highest mean platelet count.

Small WMC lesions were found in 15/20 (75%) patients, 7 of which had multiple lesions. Large lesions were found in 6 patients, and 4 had multiple lesions. One patient had both small and large lesions. Four of the 6 patients with large lesions were EBT patients. Most WMCs were identified in the frontal lobes (52%) or parietal lobes (26.4%). Three patients with EBT had extensive periventricular WMCs. (Figure S1) WMCs were less commonly noted in a few other sites - basal ganglia in 2 patients, thalamus in one and cerebellum in one patient.

In contrast to previous reports of putative “risk factors” associated with WMCs in thalassaemia (Musallam *et al*, 2012b) there was no significant difference between patients with and without WMCs in the mean haemoglobin concentration, platelet count, serum ferritin concentration or splenectomy status (Table II).

Other MRI abnormalities. In addition to WMCs, MRI scanning identified the presence of a large parietal haematopoietic mass in a 29-year-old patient with EBT who was under treatment for headaches attributed to “migraine.” Total occlusion of the right internal carotid artery, with significant collateral vessel development, was identified in another patient with EBT who did not have WMCs.

Cognitive dysfunction

A reduced cognitive score (MOCA) of 24 or lower was identified in 39/77 (50.6%) patients and 28/79 (35.4%) controls. This difference was not statistically significant ($P = 0.079$).

Lower MOCA scores were identified in 5 out of 23 (21.7%) patients with TM, 11 out of 22 (50%) with TI and 23 out of 32 (71.9%) with EBT; this association with thalassaemia phenotypes was significant ($P = 0.001$). MOCA score was also significantly reduced when patients with TI and EBT were analysed as one group, compared to TM ($P = 0.002$). There was no evidence of association between low MOCA scores and low haemoglobin level, WMC or EEG changes.

Of the 20 patients in whom WMCs were identified, 9 (56.2%) had a MOCA score below 24, which was not significantly different from the proportion (30; 49.2%) in the 62 patients without WMCs ($P = 0.823$).

Of the 39 patients with a low MOCA score, 9 (23.6%) had EEG changes, whereas 9 of the 38 patients with a MOCA score of 24 or more had EEG changes (21.9%) ($P = 1.00$).

Of the 17 patients with abnormal EEGs, 9 (52.9%) had low MOCA scores, and in the control group, one out of the 2 with an abnormal EEG (50%) had a low MOCA score.

Table II. The main differences between the patient group with WMC identified by MRI and the group without WMC.

Variable	WMC present (<i>N</i> = 20)	WMC absent (<i>N</i> = 62)	<i>P</i> value
Age	34.3 (18–65)	31.5 (10–66)	0.306
Splenectomised percentage	60%	53%	0.138
Mean haemoglobin (g/l)	69 (44.0–93.0)	75 (50.3–98.6)	0.07
Mean serum ferritin (μg/l)	1310 (152–6306)	1444 (173.5–6466)	0.332
Mean Platelet count ($\times 10^9/l$)	581 (153–1438)	452 (120–966)	0.709

The main differences between the patient group with white matter changes (WMC) identified by magnetic resonance imaging (MRI) and the group without WMC are compared in this table. None of the factors studied showed statistically significant differences. Five out of 25 β-thalassaemia major (20%) and 15/57 (26.3%) patients in the two less transfused group together had WMC. This too did not achieve statistical significance.

WMC and its association with cognition and EEG changes

The presence of WMCs was not significantly associated with a reduced cognitive score; 56.3% of patients with WMCs (9 of 16 in whom MOCA data was available) had a reduced cognitive score, and 49.2% of patients without WMCs (30 out of 61) had a reduced cognitive score ($P = 0.823$). Nor was the presence of WMCs associated with EEG abnormalities: in the 20 patients in whom WMCs were identified, five (25%) had EEG changes, while in the 61 patients without WMCs, 13 (21.3%) had EEG changes ($P = 0.761$).

Association of headache with other findings

Headache was significantly associated with WMCs on MRI. WMCs were seen in 17 (34%) of the 50 patients with headache, but in only three (9.3%) of the 32 patients without headache ($P = 0.023$). 41.1% (7/17) of the headaches in patients with WMCs were of migrainous type (three with aura and four without aura).

In contrast, no significant differences were noted in the association of headache with cognitive scores; 25 of the 50 patients with headache (50.0%) and 14 of the 32 patients without headache (43.7%) had a reduced cognitive score ($P = 0.576$). There was no significant difference in the presence of an abnormal EEG in the two groups; abnormal EEG findings were seen in 13 patients with headache (26.0%) and five patients without headache (16.1%) ($P = 0.445$).

Multiple logistic regression analysis was undertaken to determine the influence of the type of thalassaemia, presence of MRI changes, EEG abnormality, Low MOCA (score ≤ 24), low haemoglobin (Hb < 6.5), previous transfusions (more than 100 or not), and serum ferritin (more than 1000 $\mu\text{g/l}$ or not) on the presence of headaches. Type of thalassaemia was included as the first predictor variable in the model and though it was not found to be significant was retained in the model. The only predictor that was significant was presence of MRI changes ($P = 0.012$). The odds of headache were 5.7 times higher among those with MRI changes (Table S1).

Discussion

This is the largest study yet to undertake comprehensive neurological assessment, including MRI/MRA and EEG, and cognitive assessments in patients with haemoglobinopathies concurrently and compare them with a control population. Altogether, 98 MRIs were done during this study, including 82 in thalassaemia patients. This is only the second MRI study in EBT patients looking at "silent cerebral ischaemia".

There were several novel and clinically important findings in our study. The strikingly high prevalence of headaches in all types of patients with thalassaemia when compared with non-thalassaemic controls (61% vs. 22.5%) has not been previously described. There are no previously published reports of

headache prevalence in the Sri Lankan general population to compare this data with. In a community-based study from the Southern Indian state of Karnataka over a one-year period involving over 2000 individuals, headache prevalence was found to be 63.9%, with migraine contributing 25.2% to the overall burden (Kulkarni *et al*, 2015). In our study the headache prevalence amongst the thalassaemia patients was very similar to that found in the general population of Southern India and not to that in the normal controls. The variability of this data is not easy to explain but differences in the study design may be at least partly responsible.

The association of headaches with WMCs on MRI in thalassaemia patients has also not been described before. There is however an extensive literature on the association of WMCs and headache in the general population and the findings are somewhat inconsistent and contradictory. The longitudinal population-based MRI-CAMERA study suggested that female migraine sufferers were at higher risk of developing WMCs, and that this risk seemed to correlate with attack frequency and disease duration. However, a subsequent Danish population-based twin study did not find an association of WMCs, silent infarcts, and migraine with aura. Two large scale European epidemiological studies, one in France and one in Iceland, have both demonstrated an association with headache and WMC volumes, the former with 'severe headache' and the latter, most strikingly, with tension-type headache. (Kruit *et al*, 2010; Kurth *et al*, 2011; Gaist *et al*, 2016; Honningsvåg *et al*, 2018).

Our study is not in keeping with the findings of the study on children with SCD, where headache was not shown to be more common or associated with WMCs (Niebanck *et al*, 2007).

Postulating an aetiology for the headache or WMCs in patients with haemoglobinopathies is difficult based on our data. We were unable to show an association of low haemoglobin levels as the determinant of headache in thalassaemics. The difference of WMC rates between thalassaemia patients and controls (24.3% vs. 6.9%, $P = 0.078$), though statistically not significant due to the small number of MRIs undertaken among controls, is quite noteworthy. The occurrence of WMCs in the general population is well known (Weber & Knopf, 2006; Vernooij *et al*, 2007; LADIS group, 2011), and their presence among the controls albeit at a lower prevalence is not surprising. It is noteworthy that WMCs in the general population are seen more in older people. Quite in contrast, WMCs occur at a high rate in thalassaemia patients aged as young as 20 years. This may be inferred as a sign of premature ageing.

Our findings are in contrast with previous literature in several other aspects. We were unable to show the previously claimed predominance of WMCs in patients in NTDT groups as opposed to patients with β -thalassaemia major. Although our rates of WMCs are lower than the 60% incidence of WMCs in TM shown in the study by Pazgal *et al* (2016), WMCs seem to occur almost equally in the three

types of thalassaemias. The occurrence of WMCs did not seem to be associated with splenectomy or higher platelet counts, as suggested by previous studies (Musallam *et al*, 2012b). Nor was there a clear-cut association between these abnormalities and the degree of anaemia.

A low cognitive score was identified in 39/77 (50.6%) patients and 28/79 (35.4%) controls. A higher number of patients with thalassaemia had low cognitive function than normal controls although the difference did not reach statistical significance ($P = 0.079$). Contradicting previous studies, we found a low MOCA-S score in the less transfused groups of EBT and TI when compared with TM ($P = 0.002$). (Elhabiby *et al*, 2016) We were however, unable to show an association of low MOCA scores with factors such as low haemoglobin, platelet count, ferritin level or splenectomy status. Nor were we able to demonstrate an association between MRI changes and low MOCA scores. The presence of reduced cognitive function in these young patients is a matter for concern.

Although our study is the largest study to assess MRI data in patients with thalassaemias to date, and the only study to incorporate an age- and gender-matched control group, it is still limited by the number of subjects involved in the study. As this was essentially a study of older patients with thalassaemia, and the total number of adult patients, especially with the transfusion-dependent variety, is very few in Sri Lanka, recruitment of larger numbers was not possible.

Conclusions

Headaches are more common in thalassaemia patients than in the control population. WMCs occur in patients with all

types of haemoglobinopathies at a younger age than in the general population and are more likely to occur in those with headaches.

There is a higher degree of cognitive impairment in individuals with NTDT compared to those with TM irrespective of the presence of headache or WMCs.

The applicability of these findings should be tested in a larger population.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. A 35 year old patient with haemoglobin E b thalassaemia who had extensive periventricular disease on MRI. She had headache classified as TTH and a normal MOCA-S at 28 and a normal EEG.

Table S1. Risk of headache based on of logistic regression analysis.

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