β-Thalassemia intermedia: morbidity uncovered

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Brain Positron Emission Tomography In Splenectomized Adults With β-thalassemia Intermedia: Uncovering Yet Another Covert Abnormality

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Brain positron emission tomography in splenectomized adults with β-thalassemia intermedia: uncovering yet another covert abnormality

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Abstract Covert brain infarction is an emerging concern in patients with β-thalassemia intermedia (TI). We have recently observed a high prevalence (60%) of silent brain infarction on brain magnetic resonance imaging (MRI) in 30 splenectomized adults with TI. In this work, we further evaluate cerebral involvement in the same 30 patients using fluorodeoxyglucose positron emission tomography–computed tomography (PET-CT) scanning. The median age was 32 years (range, 18–54 years) with a male to female ratio of 13:17. Nineteen patients (63.3%) had evidence of decreased neuronal function on PET-CT. Involvement was mostly left sided, multiple, and most commonly in the temporal and parietal lobes. Elevated liver iron concentration, beyond 15 mg Fe/g dry weight, characterized patients with decreased neuronal function. The concordance rate between brain MRI and PET-CT for the detection of brain abnormality was only 36.7% (Kappa 0.056, P=0.757), highlighting that both modalities reveal different types of brain pathology. Decreased neuronal function is a common finding in patients with TI and is associated with iron overload. Moreover, the addition of PET-CT to MRI identifies a greater proportion of TI patients with silent neuroimaging abnormalities.

Keywords Thalassemia intermedia · Splenectomy · Brain · PET · Iron overload

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Introduction

It is now apparent that β-thalassemia intermedia (TI) carries more complexity than traditionally recognized [1]. Patients with TI have milder anemia compared to patients with β-thalassemia major (TM), usually present later in childhood, and remain largely transfusion independent [2]. However, the diagnosis of TI is now also associated with several serious morbidities like thromboembolic phenomena [3]. Hypercoagulability in TI results from a combination of several factors including a procoagulant activity of hemolyzed circulating red blood cells, increased platelet activation, coagulation factor defects, depletion of antithrombotic factors, endothelial inflammation, among others

[3]. Clinically, the risk of thromboembolic events increases with age [4–6] and is much higher in splenectomized and never-transfused patients [5–8] in whom hypercoagulability is thought to be much more prominent [7, 9]. Reported thromboembolic events were most commonly venous [5–8]. Strokes, on the other hand, are less frequent in TI compared to TM patients [6] since patients with TM have several other comorbidities that increase stroke risk like diabetes mellitus, cardiac dysfunction, and arrhythmias [10]. Nevertheless, one study showed that 37.5% of patients with TI have asymptomatic brain damage on magnetic resonance imaging (MRI) [11]. In this line, we conducted a brain MRI study on 30 splenectomized adults with TI who were neurologically intact [12]. The rate of silent brain infarcts was as high as 60%. The occurrence and multiplicity of the detected lesions were associated with older age and transfusion naivety [12]. In this current work and for the first time, we evaluate the results of brain fluorodeoxyglucose (^{18}F-FDG) positron emission tomography–computed tomography (PET-CT) scanning in the same 30 patients to further understand cerebral involvement in this patient population.

Materials and methods

Patients

This was a cross-sectional study conducted on all splenectomized TI patients aged 18 years or older (n=43) attending the Chronic Care Center (Lebanon) between June and December 2008. All patients were diagnosed with TI based on described criteria [13]. None of the patients had Hb S, Hb C, Hb E/β, or δβ-thalassemia, coinheritance of α-thalassemia, or coinheritance of determinants associated with increased γ chain production. Exclusion criteria, actively screened for, are summarized in Table 1. After screening patients for exclusion criteria, 30 patients were found eligible and were recruited in the study. The study was approved by the institutional review board of the center and written consents were obtained from all patients.

Patient charts were reviewed for demographics (age and gender) and any history of transfusion therapy. Blood samples were obtained for the assessment of total hemoglobin level, platelet counts, and steady-state serum ferritin levels. Direct determination of liver iron concentration (LIC) was performed by R2 MRI using established methodology [14]. Brain MRI and PET-CT studies were done for all patients on the same day.

Brain MRI

Brain MRIs were conducted as previously published [12]. In brief, they were performed on a 3.0-T, eight-channel head coil, Achieva Philips Scanner using axial T1-weighted images (repetition time/echo delay time (TR/TE), 450/10), T2-weighted gradient echo images (TR/TE, 731/16), fluid-attenuated inversion recovery (FLAIR) images (TR/TE, 11,000/125), and diffusion-weighted imaging (TR/TE, 2,312/68). Coronal FLAIR images (TR/TE, 11,000/125) as well as coronal and sagittal T2-weighted images (TR/TE, 3,000/80) were also obtained. No contrast material was administered. Two blinded neuroradiologists reviewed the studies, looking for ischemic lesions. Infarction or ischemic lesions were defined as areas of abnormally increased

Table 1 Exclusion criteria

Criterion	Definition and assessment method
Neurological and/or gross cognitive signs or symptoms	Abnormality detected during medical history taking, neurological exam, or MMSE performed by a qualified neurologist (AB)
Use of anticoagulant or antiplatelet therapy	Any current or previous history of anticoagulant or antiplatelet therapy
Diabetes	Use of antidiabetic drugs or a fasting blood sugar ≥126 mg/dl
Hypertension	Use of antihypertensive drugs or a blood pressure ≥140/90 mmHg on two readings 6 weeks apart
Cardiac disease	Any abnormality on electrocardiography or echocardiography including: arrhythmias, valvular disease, dysfunction, presence of atrial or ventricular thrombi, or pulmonary hypertension
Carotid stenosis	Evidence of >50% narrowing of the carotid(s) on color-flow duplex scanning
Thrombophilia	Evidence of factor V Leiden, prothrombin, or MTHFR mutations on genetic studies; or abnormality in protein C, protein S, antithrombin III, lupus anticoagulant, or cardiolipin antibodies levels
Smoking	Any current or previous history of smoking

MMSE mini mental status exam, *MTHFR* methyletetrahydrofolate reductase

signal intensity on the T2- and FLAIR-weighted sequences and were classified by anatomic location.

PET-CT

Brain PET-CT was done on the same day as MRI for all patients. Before undergoing PET-CT, patients were asked to fast for at least 6 h, although oral hydration with glucose-free water was allowed. After ensuring a normal blood glucose level in the peripheral circulation, the patients received an intravenous injection of 370 MBq (10 mCi) ^{18}F-FDG and allowed to rest for 45 min before undergoing scanning. Scans were acquired with a PET scanner combined with a multisection CT scanner (Biograph 6, Siemens). The axes of the two systems were mechanically aligned such that a patient can be moved from the CT to the PET gantry by moving the examination table. CT scanning of the brain was performed according to a standardized protocol, and immediately afterwards, PET scanning was performed with the identical transverse field of view. The acquisition time for PET in static mode was 30 min. The CT data were resized from a 512×512 to a 128×128 matrix to match the PET data so that scans can be fused and CT-based transmission maps generated. PET data sets were reconstructed iteratively using an ordered subset expectation maximization algorithm with segmented attenuation correction. Coregistered scans were then displayed on a workstation with commercially available software (e.soft from Siemens). Visual assessment was determined by two blinded nuclear medicine physicians. Visual (qualitative) interpretation was based on the subjective impression of the degree of ^{18}F-FDG uptake. Decreased uptake was defined as the relative decrease in ^{18}F-FDG uptake in a lobe compared to other lobes, which reflects a decrease of neuronal function (glucose utilization). Review was done independently, and in case of disagreement (two cases), the two experts reviewed the images jointly until a consensus was reached.

Statistical analysis

Descriptive data are presented as medians (range) or percentages. Bivariate correlations between PET-CT abnormality and study parameters were evaluated using the Mann–Whitney *U* test, the Chi-square test, and the Fisher's exact test. A logistic regression analysis was performed to evaluate the probability of a decreased neuronal function on PET-CT, using the variable found to be statistically significant in the bivariate analysis as an independent continuous variable. To determine the optimal variable cutoff for the logistic regression equation that best predicts PET-CT abnormality, receiver operating characteristic (ROC) curve analysis was performed [15]. A concordance Kappa value was calculated for the agreement between brain MRI and PET-CT for the detection of abnormalities. A Kappa value of 1 indicates complete agreement and a value of 0 indicates no agreement at all. All *P* values were two-sided with the level of significance set at <0.05.

Results

Patients' characteristics

A total of 30 patients were included in the analysis. The median age was 32 years (range, 18–54 years) with a male to female ratio of 13:17. Most patients were transfusion independent (n=18, 60%) while 12 patients (40%) were occasionally transfused during infections, surgery, or pregnancy. None of the patients were on iron chelation or hydroxyurea therapy. The median total hemoglobin level was 84 g/l (range, 49–131 g/l) and the median platelet count was 789.5×10^9/l (range, 189–$1{,}602\times10^9$/l). The median serum ferritin level was 1,127.5 μg/l (range, 116–3,158 μg/l) and the median LIC was 10.75 mg Fe/g dry weight (dw) (range, 1–32.1 mg Fe/g dw).

PET-CT

Nineteen patients (63.3%) had evidence of decreased neuronal function on PET-CT. Only 1 patient had bilateral brain involvement while the remaining 18 had left brain involvement. Five (26.3%) out of the 19 patients had single lobe involvement while 14 (73.7%) had multiple lobes involved (11 had two, 3 had three lobes involved). The temporal lobe was most commonly involved (n=18, 94.7%), followed by the parietal (n=14, 73.7%) and frontal lobes (n=3, 15.8%). The occipital lobe was not involved in any patient.

Risk factors for decreased neuronal function

There was no statistically significant correlation between the evidence of decreased neuronal function on PET-CT and any of age, gender, transfusion history, total hemoglobin level, or platelet count. The median serum ferritin level was higher in patients with PET-CT abnormality than those without (1,215 vs. 861.5 μg/l), although the association did not reach statistical significance (P=0.053). Moreover, the median LIC was significantly higher in patients with evidence of decreased neuronal activity than those without (16.3 vs. 3.4 mg Fe/g dw, P=0.003). A logistic regression model was also performed to estimate the probability of abnormality on PET-CT using LIC as an independent variable (Fig. 1). The model was significant (P<0.001) and had a predictive value of 76.7%. On ROC curve

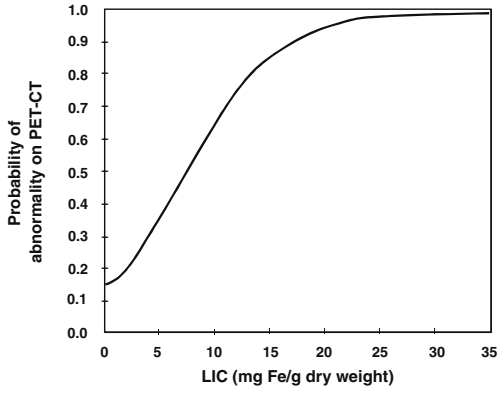

Fig. 1 Logistic regression curve showing the probability or PET-CT abnormality as a function of LIC

analysis, a LIC cutoff of 15 mg Fe/g dw was the best predictor of decreased neuronal function on PET-CT with an area under the curve of 0.828±0.075 (95% confidence interval 0.681–0.975, P=0.003), a sensitivity of 52.6%, and a specificity of 100%.

PET-CT vs. brain MRI

Among the group of 30 patients, 18 (60%) had evidence of silent infarcts on brain MRI, all in the white matter [12]. A total of 11 patients (36.7%) had evidence of brain abnormality on both MRI and PET-CT while 26 patients (86.7%) had evidence of brain abnormality on either MRI or PET-CT (Table 2). The concordance rates between brain MRI and PET-CT were 36.7% for the detection of abnormality (Kappa 0.056, P=0.757); 23.3% for the detection of multiple abnormalities (Kappa 0.062, P= 0.732); 3.3% for the detection of bilateral brain abnormality (Kappa 0.086, P=0.245); and 6.7% (Kappa 0.036, P= 0.713), 10% (Kappa 0.164, P=0.338), 3.3% (Kappa 0.045, P=0.406), and 0% (Kappa N/A, P = N/A) for the detection of frontal, parietal, temporal, or occipital abnormalities, respectively (Fig. 2).

Discussion

Unlike MRI, PET-CT imaging does not seem helpful in detecting silent white matter infarcts in patients with TI. Nevertheless, PET-CT imaging revealed that decreased neuronal function is a common finding in this patient population, which is associated with iron overload. Thus, the addition of PET-CT to MRI identifies a greater proportion of TI patients with silent neuroimaging abnormalities and provides additional information on the neurophysiologic status of these patients.

The association of iron overload, evident from the elevated LIC, with decreased neuronal function on PET-CT in our study is the first report of its kind for patients with hemoglobinopathies. Transfusion-independent patients with TI still develop iron overload due to increased intestinal absorption and show considerably high levels of LIC [16, 17], which may explain why both transfused and nontransfused patients had similar rates of PET-CT abnormality in our study. Although cardiac siderosis and disease do not seem to be a consequence of iron overload in this patient population [18–20], an association with other clinical complications in several organ systems has been observed [5]. Although a causal relationship may be hard to confirm, our study adds brain involvement to the growing list of iron overload-related morbidity in TI patients. Iron is an essential element for the multiple functions of the brain. The abnormal distribution of brain iron has been implicated in neuronal injury and death in several neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis. Multiple iron chelators have been shown to possess neuroprotective and neuro-

Table 2 Brain abnormalities as detected by MRI or PET-CT in the 30 patients

Parameter	MRI [12]	PET-CT	Both MRI and PET-CT	Either MRI or PET-CT
Abnormal finding	18 (60)	19 (63.3)	11 (36.7)	26 (86.7)
Number of abnormalities				
Single	4 (13.3)	5 (16.7)	1 (0)	8 (26.7)
Multiple	14 (46.7)	14 (46.7)	7 (23.3)	21 (70)
Bilateral abnormality	13 (43.3)	1 (3.3)	1 (3.3)	13 (43.3)
Location of abnormality				
Frontal	17 (56.7)	3 (10)	2 (6.7)	18 (60)
Parietal	9 (30)	14 (46.7)	3 (10)	20 (66.7)
Temporal	1 (3.3)	18 (60)	1 (3.3)	18 (60)
Occipital	3 (10)	0 (0)	0 (0)	3 (10)

MRI magnetic resonance imaging, *PET* positron emission tomography, *CT* computed tomography

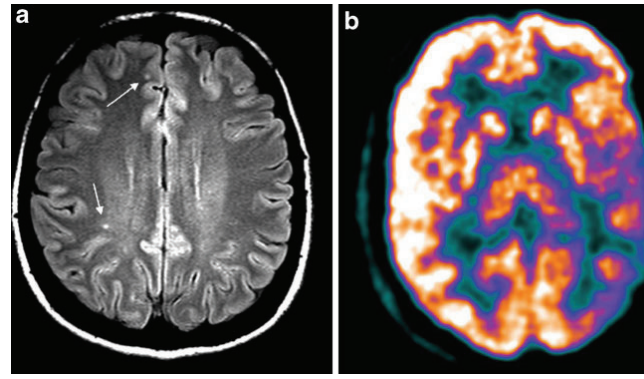

Fig. 2 Example of poor concordance between brain MRI and PET-CT. A 30-year-old female with **a** two ischemic lesions (<0.5 cm, *arrows*) in the right frontal and parietal lobes on MRI and **b** hypometabolism in the left parietal and temporal lobes on PET-CT

restorative properties in these diseases, suggesting that iron chelation might be promising therapeutics [21]. Whether the same applies for patients with TI merits further evaluation. The risk factors for silent brain infarcts detected on MRI remain different. There is no evidence that iron overload can be associated with cerebral small vessel disease or silent infarcts [12]. In fact, transfusion therapy seems to be protective against the development of these silent white matter lesions [12], probably due to the beneficial role of transfusions in improving hypercoagulability and vascular disease in TI by decreasing the concentrations of damaged red blood cells with thrombogenic potential, among other factors [3]. Although the occurrence and multiplicity of silent brain infarcts increase with age in TI patients [12], such observation was not noted for the decrease in neuronal function detected on PET-CT. In line with our findings, it could be hypothesized that neuronal damage could occur early on with direct iron toxicity, unlike vascular damage where the accumulation of risk factors over time may be necessary.

Most acquired knowledge on cerebral involvement in hemoglobinopathies comes from studies on patients with sickle cell disease (SCD) [22]. The application of PET in SCD subjects was first published in 1988 in a preliminary study on six adults who had no history of neurological events but were found to have significant glucose hypometabolism in the frontal areas of the brain [23]. Our finding that MRI and PET-CT reveal different types of silent brain pathology (thus the low concordance rate) is in agreement with a similar study on patients with SCD [24]. Among 30 patients with no evidence of neurological dysfunction, 13 (43%) patients were found to have silent brain infarcts on MRI. PET identified 12 additional subjects, with normal MRI, to have silent brain abnormality (total=83%). Two valid questions are (1) why would PET-CT fail to reveal silent brain infarcts detected on MRI and (2) can patients with decreased neuronal function on PET-CT have normal MRI? First, in the aforementioned study on patients with SCD [24], the concordance rate between abnormal PET and MRI scans was 80% for MRI-identified gray matter lesions, dropping to ~50% for white matter lesions [24]. These observations may be partly attributed to the naturally low glucose utilization in the white matter and could explain the low concordance for silent stroke detection between both imaging modalities, especially in our study where all silent MRI lesions were detected in the white matter. Thus, PET imaging cannot replace MRI to identify white matter lesions in the watershed areas [25–28]. Second, the areas of functional abnormality are usually greater than the structural neuronal loss defined by MRI or CT; thus, PET-CT abnormality can be detected with a normal MRI [29]. Moreover, there was a low concordance rate for the location of abnormality between both imaging techniques. Silent infarcts on MRI were bilateral and most commonly involved the frontal and parietal lobes, whereas neuronal dysfunction evident on PET-CT was mainly left sided, involving the parietal and temporal lobes. Although this may be attributed to the aforementioned difference in the type of brain pathology revealed by the two imaging modalities, it still warrants further discussion. The diffuse nature of silent infarcts on brain MRI in our study and their high prevalence in the frontal and parietal white matter is in total agreement with studies on SCD patients [30, 31]. In SCD patients, it was shown that the geographic distribution of the involved small penetrating arteries in the brain is derived from the carotid rather than the vertebrobasilar circulation, as a result of several anatomic and hemodynamic factors [32]. However, PET-CT abnormalities in this study were mostly detected in the temporal and/or parietal lobes. Temporoparietal hypometabolism on ^{18}F-FDG PET is indeed the classic metabolic abnormality associated with Alzheimer's neuronal dysfunction [33], which has been associated with selective iron accumulation and oxidative damage [34, 35]. Whether a similar mechanism applies in

patients with TI warrants further pathological investigation. However, the finding that PET-CT abnormalities in patients with TI are mainly confined to the dominant, left hemisphere (all patients in this report were right-handed) is difficult to interpret using the available evidence. Nevertheless, it may still be attributed to chance, considering the small sample size in this study.

The main limitation of our study is the lack of neurocognitive testing. Despite the terminology, "silent infarcts" observed on brain MRI are clinically significant given their association with subsequent overt stroke and neurocognitive deficits, as evident from studies in children and adults with SCD [30, 36–41]. Decreased neuronal function on PET scanning in patients with SCD is also associated with an intelligence quotient lower than the normal mean [24, 28] and a broader region of cerebral dysfunction that may be a prelude to clinical stroke [42, 43]. Whether such correlations exist in patients with TI merits evaluation.

In conclusion, our study demonstrated that decreased neuronal function evident on PET-CT is common in patients with TI, especially those characterized by elevated LIC. Moreover, it seems that the combined use of PET-CT and MRI could better identify splenectomized TI adults at high risk for stroke or functional neurologic deficits by highlighting the extent of physiologic dysfunction alongside the anatomic loss of neuronal tissue. However, larger studies are needed to confirm these findings before recommendations for screening can be made and to avoid unnecessary radiation exposure. More importantly, the exact mechanisms behind these abnormalities should be understood and their correlation with neurocognitive and long-term sequelae should be prospectively examined, thus allowing for optimal risk classification and timely preventive intervention.

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Conflicts of interest ATT is a member of Novartis Speakers' Bureau.

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