Regional cerebral blood flow in patients with sickle cell disease: study with single photon emission computed tomography

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Abstract
Objective Neurological complications have been reported in patients with sickle-cell disease (SCD) using positron emission tomography (PET), magnetic resonance imaging (MRI), and computed tomography (CT), but not with single photon emission computed tomography (SPECT). The objective of this study was to investigate brain perfusion in the patients with SCD using SPECT after technetium-99m hexamethylpropylene amine oxime (99mTc-HMPAO), was administered and compare the findings with those of demography, physical examination, MRI and hematological profile.

Methods The study involved 21 patients (12 males, 9 females, age at study 8–45 years) who were known to be having SCD for a duration of at least 5 years. The patients were not in acute crisis and had normal neurological assessments with no known history of stroke or transient ischemic episode or previous abnormal CT or MRI brain scan, and were right-handed. The brain SPECT was performed after intravenous injection of 740 MBq (20 mCi) 99mTc-HMPAO in adults or an appropriate dose in pediatric patients. The scans were visually interpreted by two nuclear medicine physicians and a decision was reached by consensus. An MRI done 3 months later was interpreted by a radiologist. The demographic data and hematological profile were obtained from the medical records of the patients.

Results Of the 21 patients, 7 (age 11–22 years) had brain perfusion deficit mostly in the frontal lobe either alone or in combination with temporal and/or parietal lobe. The MRI was abnormal in 2 patients. The brain perfusion deficit was not associated with the demographic data of the patients or hematological profiles.

Conclusions The findings show that SPECT was useful in detecting brain perfusion deficit in SCD patients, and such an early detection may be clinically useful in the subsequent follow-up of such patients, since it is known that cerebral perfusion deficit can lead to silent infarct and/or overt stroke, and affect cognitive skills.

Keywords SPECT · Regional cerebral blood flow · Sickle cell disease · Te99mHMPAO · MRI

Introduction
Sickle-cell disease is a hemolytic anemia characterized by abnormally shaped (sickled) red blood cells (RBCs) that result from a point mutation on the 6th amino acid in the β-chain; valine is substituted for glutamic acid [1]. It follows a highly variable clinical course; some patients die in infancy from disabling effects of recurrent crises
or overwhelming infection; others may live a normal lifespan. The most common complication is the painful vaso-occlusive crisis, precipitated by infection, dehydration, or exposure to cold. One of the complications of acute crises is brain syndrome. Brain syndrome is particularly common in childhood, often presenting as a stroke, although it may be preceded by a variety of bizarre neurological syndromes similar in nature to transient ischemic attacks. There is a tendency for these episodes to recur and there may be permanent neurological damage [1]. Stroke has been the most devastating and feared neurologic complication of sickle cell hemoglobinopathy since it was first reported in a 5-year-old child in 1923 [2]. Despite subsequent intense interest, many questions remain unanswered about the incidence of neurologic complications, the neuropsychological sequelae, identification of risk factors, and methods of prevention [2]. Children with sickle cell anemia (HbSS) are at high risk of stroke and are associated with neuropsychometric deficit [3, 4]. The incidence of strokes per year during the first two decades of life is approximately 0.7%, and 80% of the strokes are due to cerebral infarctions [5]. The complications appear early in life; 80% occur before the age of 15, and the average age of onset is 6. The strokes result in hemiplegia, seizures, speech defects, and visual disturbances, all of which adversely affect intellectual and academic functioning [6].

The neurological complications of sickle-cell disease have been studied using positron emission tomography [7], magnetic resonance imaging [3], computed tomography [3], magnetic resonance angiography [8], transcranial Doppler, and ultrasound imaging [9]. Other than a case report [10] and a letter to an editor [11], single photon emission computed tomography (SPECT) has not been mentioned as being used to study cerebral perfusion in SCD patients. In the letter to the editor, Parsa et al. [11] recommended further studies to establish the role of SPECT imaging in the clinical assessment of patients with SCD [11]. Equally important, SPECT brain perfusion imaging has proven useful for investigating cerebrovascular diseases [2, 12–14], dementia [14], cancer [12], evaluating brain trauma [12], psychiatric disease [12, 14], drug toxicity [14–17], and also seizure workup of patients [2, 14]. Therefore, the aim of this study was to use the $^{99m}$Tc-HMPAO SPECT brain perfusion imaging technique to investigate brain perfusion deficits in a group of patients with SCD and to compare the findings with those of demography, physical examination, MRI, and hematological profiles.

Patients and methods

Patients

Twenty-one patients (12 males and 9 females, current age 8–45 years) with sickle cell disease were referred from different hospitals in Kuwait by hematologists. At diagnosis, 4 patients were less than 1 year old; 9 patients, 2–3 years; 3 patients, 3–5 years; and 5 patients more than 5 years old. None of the patients was in acute crisis at the time of the study. The last admission to the hospital prior to the study was at least 7 days. The patients had a diagnosis of SCD of a duration of at least 5 years with normal neurological assessments and were right-handed. None of the patients had any known history of stroke or transient ischemic attack (TIA), or previous abnormal CT or MRI brain scan that would have indicated a previous history of head trauma. A written informed consent was obtained directly from all the adult patients and indirectly from the parents of pediatric patients. The general demographic data and medical history were obtained, clinical examinations were performed, and all were recorded on a data sheet.

No specific patient preparation was required, but the patient was evaluated for the ability to cooperate with the study. Prior to the injection, a constant environment was maintained by having the patient in a quiet room with dim light, eyes closed, and no background noise. The patient was instructed not to speak, read, or have any interaction with other persons.

Brain SPECT imaging

The $^{99m}$Tc-HMPAO (exametazime) complex was prepared by mixing a freeze-dried formulation of the ligand containing stannous chloride with 1.1–2.96 GBq (30–80 mCi) in 5 ml saline of fresh generator eluate (<2 h old) according to the manufacturer’s instructions (Amersham International, Amersham, UK) [18].

The patient’s antecubital vein was cannulated 15 min before starting the study. Ten minutes later, the patient was intravenously injected with 740 MBq (20 mCi) of $^{99m}$Tc-HMPAO for an adult and an appropriate fractional dose (on the basis of weight and age) for a pediatric patient. $^{99m}$Tc-HMPAO was injected within 30 minutes of its preparation because it is known that after 30 min, preparations are converted to a less lipophilic (secondary) form that does not cross the blood-brain barrier [19, 20].

The patients were positioned supine on the imaging table with the head stabilized in a neutral position in a head-holder to avoid possible motion. A dual-head GE