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Original Article

99mTc-ECD brain perfusion SPECT imaging for the assessment of brain perfusion in cerebral palsy (CP) patients with evaluation of the effect of hyperbaric oxygen therapy

Mina Taghizadeh Asl[1], Farzaneh Yousefi[2], Reza Nemati[2], Majid Assadi[3]

[1]Department of Nuclear Medicine, Kasra Hospital, Tehran, Iran; [2]Department of Neurology, Bushehr Medical University Hospital, Bushehr University of Medical Sciences, Bushehr, Iran; [3]The Persian Gulf Nuclear Medicine Research Center, Bushehr University of Medical Sciences, Bushehr, Iran

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Abstract: Objective: The present study was carried out to evaluate cerebral perfusion in different types of cerebral palsy (CP) patients. For those patients who underwent hyperbaric oxygen therapy, brain perfusion before and after the therapy was compared. Methods: A total of 11 CP patients were enrolled in this study, of which 4 patients underwent oxygen therapy. Before oxygen therapy and at the end of 40 sessions of oxygen treatment, 99mTc-ECD brain perfusion single photon emission computed tomography (SPECT) was performed , and the results were compared. Results: A total of 11 CP patients, 7 females and 4 males with an age range of 5-27 years participated in the study. In brain SPECT studies, all the patients showed perfusion impairments. The region most significantly involved was the frontal lobe (54.54%), followed by the temporal lobe (27.27%), the occipital lobe (18.18%), the visual cortex (18.18%), the basal ganglia (9.09%), the parietal lobe (9.09%), and the cerebellum (9.09%). Frontal-lobe hypoperfusion was seen in all types of cerebral palsy. Two out of 4 patients (2 males and 2 females) who underwent oxygen therapy revealed certain degree of brain perfusion improvement. Conclusion: This study demonstrated decreased cerebral perfusion in different types of CP patients. The study also showed that hyperbaric oxygen therapy improved cerebral perfusion in a few CP patients. However, it could keep the physiological discussion open and strenghten a link with other areas of neurology in which this approach may have some value.

Keywords: Cerebral palsy (CP), 99mTc-ECD brain perfusion SPECT, hyperbaric oxygen therapy

Introduction

Cerebral palsy (CP) is a nonprogressive disease that presents as a disorder of motion and posture following brain injury during a period of development. Hypoxic-ischemic encephalopathy (HIE) is one of the major causes of the disability entity [1].

There is no specific diagnostic test for the diagnosis of CP except careful physical examinations [2]. Anatomic imaging may be a useful modality in the diagnosis and detection of brain lesions in CP patients; 82% of patients who were born prematurely and 55% of patients born at term have abnormal structural findings on magnetic resonance imaging (MRI) [1].

On the other hand, functional imaging is able to detect brain lesions in CP cases in which lesions were not detectable using conventional MRI. A PET study showed focal areas of cortical hypometabolism in the absence of apparent structural abnormalities [3]. Single photon emission computed tomography (SPECT) is a useful method to detect cerebral lesions that are not detectable in patients with CP by MRI [4].

The present study was designed to evaluate the brain perfusion SPECT of patients with CP and to compare the results with their clinical features. There is no study to date based on the evaluation of SPECT of patients with CP who received oxygen therapy; therefore, this study included an evaluation of the changes of

SPECTs before and after oxygen therapy in patients with CP.

Materials and methods

Participants and study design

The study population consists of 11 patients (4 males and 7 females with an age range of 5-27 years) with CP following perinatal asphyxia that was diagnosed by physical examinations and laboratory tests, including electroencephalography and electromyography. The patients were referred from the neurology department to our center for the assessment of brain perfusion between May 2010 and December 2012. Patients with cerebral palsy of postneonatal onset were excluded, as were those with other causes of encephalopathy. Children who had experienced one recent episode (within 1 month) of acute otitis or those with chronic otitis (three episodes or more within the previous year) were excluded, as were those with any condition that put them at risk for complications of hyperbaric oxygen (e.g., asthma, convulsions). Children with behavioral problems, or those recently treated with botulinum toxin or orthopedic surgery (within the past 6 months) or dorsal rhizotomy within the past 2 years, were also excluded. Previous exposure to hyperbaric oxygen was also an exclusion criterion. Antispasticity medication, drugs affecting concentration, and physiotherapy were stopped 6 weeks before the trial.

Among the 11 patients, there were 4 who met these criteria and who were undergoing oxygen therapy. Hyperbaric oxygen treatment consisted of 100% oxygen at a pressure of 1.75 atm absolute (ATA) for 60 minutes. A complete intervention comprised 40 sessions: once per day, 5 days per week, for 8 weeks. At the end of 40 sessions of oxygen therapy, brain SPECT was performed again; the results were then evaluated and compared with previous SPECT results.

This study complies with the Declaration of Helsinki and was approved by our institutional ethics committee; all patients' parents gave written informed consent.

Imaging protocols

All patients underwent 99mTc-ECD brain SPECT scan and a dose of 99mTc-ECD based on the patient's weight. The administered activity of 99mTc-ECD was 0.2-0.3 mCi/Kg. A commercial ECD kit (AEOI, Tehran, Iran) was used, and the labeling and quality control procedures were performed according to the manufacturer's instructions. The radiochemical purity was calculated by comparing the peak for the 99mTc-ECD complex to the sum of all other peaks on the plate. The radiochemical purities of 99mTc-ECD were higher than 97%.

All subjects had an intravenous (IV) line established while they were lying down, with their eyes closed and ears unplugged, in a quiet, darkened room with low ambient sound and light. After approximately 30 minutes, each subject received an 800-MBq IV injection of tracer while they were still lying down in the same quiet, darkened room. One hour after an IV injection of 800 MBq 99mTc-ECD in a room with a low level of ambient light and minimal background noise, the SPECT procedure was performed. Scans were performed using a dual-head gamma camera (Siemens, Germany) that was equipped with a pair of low-energy and high-resolution collimators. The full width at half maximum (FWHM) of this system, as measured in-house, was 12-mm for Tc-99m. Standard head positioning was based on a uniform alignment of the external auditory meatus using automated table positioning and camera-to-head-detector ratio values. The total acquisition time was 35 minutes for each study. Images were acquired in a 64 _ 64 _ 64 three-dimensional pixel matrix at 64 steps, 30 seconds per step. Before reconstruction of the images, attenuation correction of the images was carried out by the Chang method (attenuation coefficient 0.12 cm_1). The data were then processed by back projection and filtered with a Butterworth filter, using a Nyquist frequency cut-off of 0.5 and order of 5. Images were reconstructed and displayed in all three orthogonal planes.

Image interpretation

Scintigraphic results were analyzed by two experienced nuclear medicine physicians who were not aware of the patients' medical histories; differences of judgment were resolved by consensus. The frontal, parietal, temporal, occipital cortex, basal ganglia, brainstem, and cerebellum were analyzed systematically. Normal brain SPECT findings included homoge-

Table 1. Demographic data and results of 99mTc-ECD brain SPECT in every cerebral palsy patient

Case	Sex	Age	Cp type	Visual cortex	Frontal	Occipital	Temporal	Parietal	Cerebellum	Cortex	Subcortex
1	M	11	SP		+	+			+		
2	M	6.5	SP				+				
3	F	12	C							+	+
4	F	22	C		+						
5	F	27	SQ	+							
6	F	26	SD		+	+	+				
7	F	5	SQ		+					+	+
8	F	10	SP							+	
9	M	7	SQ		+			+			+
10	F	23	SD		+		+				
11	M	24	SP	+							+

SP, spastic paraplegic; C, choreathetoid; SQ, spastic quadriplegic; SD, spastic diplegic.

neous rCBF in the mentioned regions without focal hypoperfusion or visible asymmetry. Abnormal brain SPECT findings were defined as heterogeneous rCBF with focal hypoperfusion or visible asymmetry in at least two consecutive slices in two sections.

Results

The patients were grouped into one of the following major clinical subtypes based on the predominant features of their motor impairments: spastic diplagia (n = 2), spastic quadriplagia (n = 3), spastic paraplegia (n = 4), and choreathetoid (n = 2) (**Table 1**).

On the SPECT study, all patients showed perfusion impairments. The region most significantly involved was the frontal lobe (54.54%), followed by the temporal lobe (27.27%), the occipital lobe (18.18%), the visual cortex (18.18%), the basal ganglia (9.09%), the parietal lobe (9.09%), and the cerebellum (9.09%) (**Table 1**).

Frontal lobe hypoperfusion was seen in all types of cerebral palsy. Cerebral cortex hypoperfusion was seen in all types of cerebral palsy except diplagia. Hypoperfusion of the basal ganglia and of the cerebellum was seen in just 25% of the patients with spastic paraplegia. Parietal lobe hypoperfusion was observed in just 33% of the patients with spastic quadriplegia.

Among the 11 patients, 4 (2 males and 2 females) underwent oxygen therapy, after which two of them revealed some degree of brain perfusion improvement (**Table 2**) (**Figures 1** and **2**).

Discussion

Our study showed abnormal perfusion scans in all patients with CP. Although specific perfusion defects were not detected for every type of CP, some areas involved were more common than others in one type. The basal ganglia was involved in all patients with the choreathetoid type. Extratemporal cortices, particularly frontal, commonly showed hypoperfusion in the spastic quadriparetic type. In the spastic diplegia type, the temporal, as well as the extratemporal cortices showed abnormalities.

Based upon the pattern of motor impairment, CP is classified into several clinical subtypes: spastic quadriparesis, spastic diplegia, spastic or infantile hemiplegia, and an extrapyramidal variant with choreoathetoid or dystonic features. Generally, patients are placed in a particular subtype based upon predominant clinical manifestations during examination, although overlapping features in patients are common [5].

The pattern of hypoxic brain damage following perinatal asphyxia is different, depending on the gestational age of the fetus at the time the injury occurred [6]. In premature infants, the main pattern of damage is periventricular leukomalacia (PVL), which is characterized by a loss of periventricular white matter and associated with ventriculomegaly. In addition, PVL may be distributed to affect areas of white matter other than periventricular [6]. At the neonatal stage, asphyxia involves neocortical and subcortical white matter and also the basal ganglia, including the thalamus, the putamen, the globus pallidus, and the caudate nucleus. The clinical picture of CP is related to the distribution of cerebral lesions. Spastic diplegia is associated with PVL. In cases where lesions extend to the subcortical area, patterns of tetraplegia are seen that are frequently associat-

Table 2. Brain perfusion SPECT data of cerebral palsy patients who underwent oxygen therapy

Case	Sex	Age	CP type	SPECT before	SPECT after	Change
1	F	12	C	Mild diffuse cortical and subcortical hypoperfusion	normal	Yes
2	F	27	SQ	Moderate hypoperfusion confined to left visual cortex	Moderate hypoperfusion confined to left visual cortex	No
3	M	7	SQ	Moderate hypoperfusion through the frontal and parietals lobes and also caudate nucleus (R > L)	Mild hypoperfusion through the frontal and parietals lobes and also caudate nucleus (R > L)	Yes
4	M	24	SP	Moderate hypoperfusion of the right visual cortex with extension to the occipital zone and moderate bilateral hypoperfusion of the subcortical structures	Moderate hypoperfusion of the right visual cortex with extension to the occipital zone and moderate bilateral hypoperfusion of the subcortical structures	No

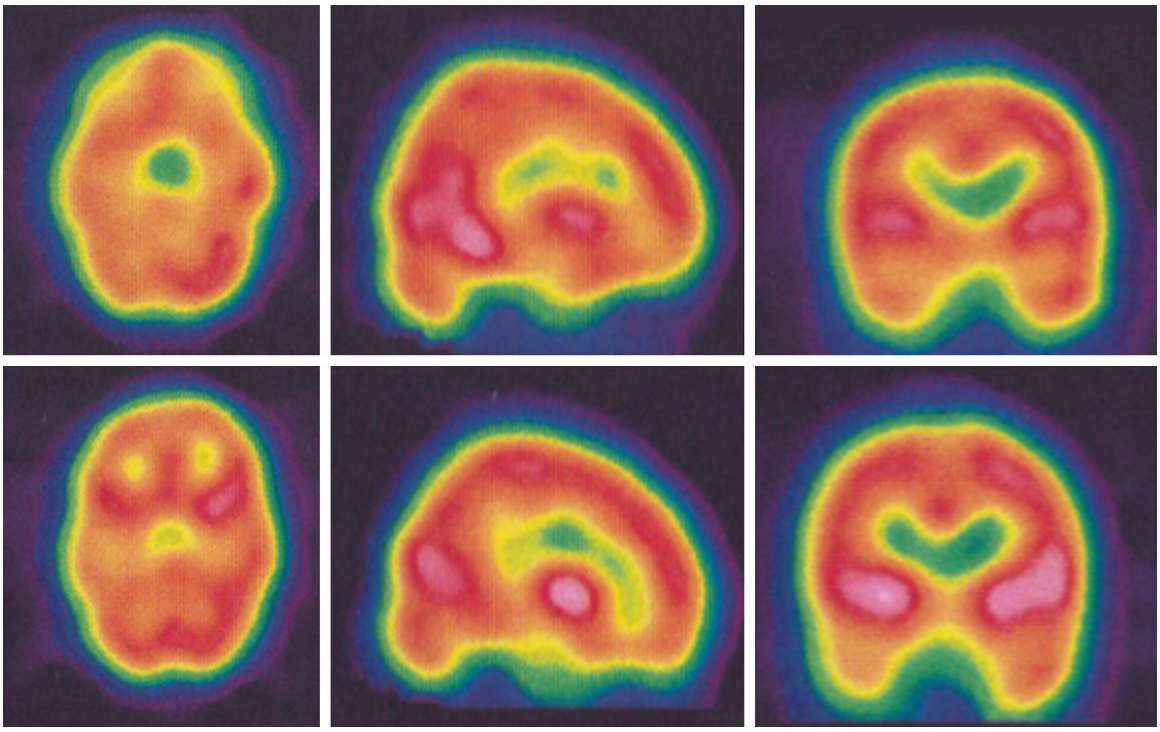

Figure 1. Pre-treatment (upper rows) and post-treatment (lower rows) SPECT images of a 12-year-old CP patient. There is a mild diffuse cortical and subcortical hypoperfusion on pretreatment 99mTc-ECD brain perfusion SPECT, which is normalized after O2 therapy. The left columns indicate transvers 99mTc-ECD SPECT images; the middle columns indicate sagittal 99mTc-ECD SPECT images; and the right columns indicate coronal 99mTc-ECD SPECT images.

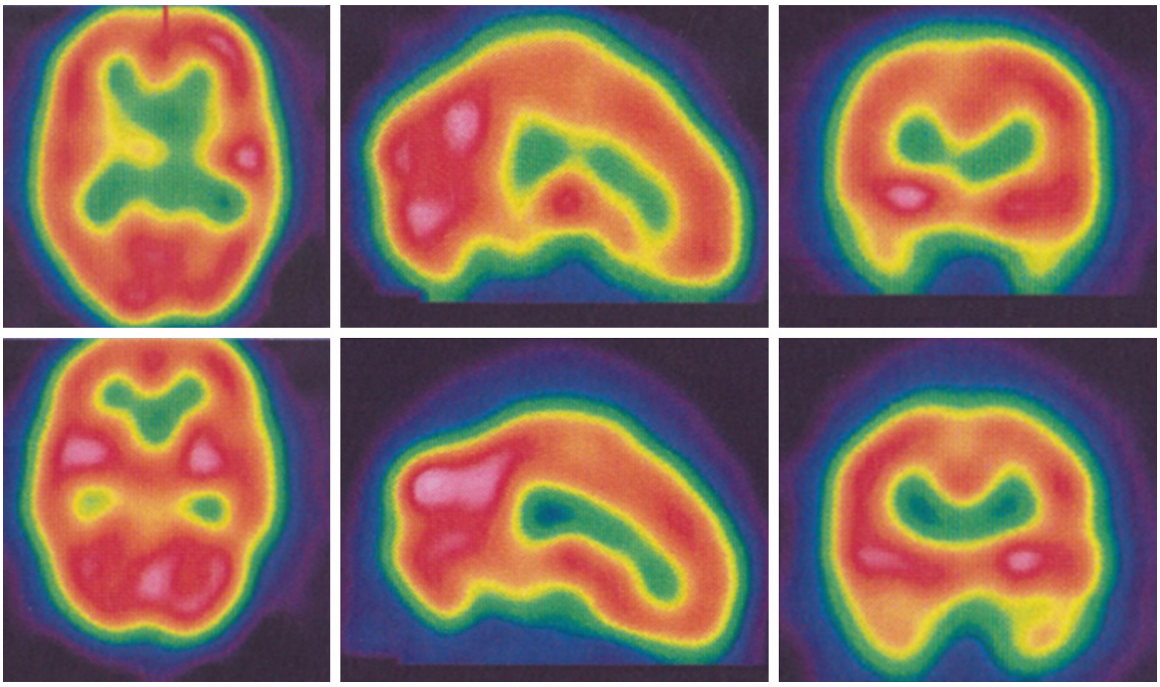

Figure 2. Pre-treatment (upper rows) and post-treatment (lower rows) SPECT images of a 7-year-old CP patient. There is a moderate hypoperfusion through the frontal and parietals lobes and also caudate nucleus (R > L) on pretreatment 99mTc-ECD brain perfusion SPECT, which is partially reperfused after O2 therapy. The left columns indicate transvers 99mTc-ECD SPECT images; the middle columns indicate sagittal 99mTc-ECD SPECT images; and the right columns indicate coronal 99mTc-ECD SPECT images.

ed with mental retardation and epilepsy. Involvement of the basal ganglia results in additional extrapyramidal symptoms [6].

Decreased periventricular white matter and increased signals in the region, with close approximation of the posterior temporal and occipital cortices to the ventricular wall, are characteristic MR findings of PVL in HIE [1]. Other MRI findings include abnormalities in the temporal and extratemporal cortices, thalamic abnormality, and basal ganglia and cerebellar atrophy [1].

Lee et al. investigated cerebral perfusion in 51 patients with different types of CP and reported that thalamic hypoperfusion was present in nearly all cases, and in also every type. Other perfusion abnormalities revealed in the study were detected the temporal lobe, cerebellum, basal ganglia, and extratemporal and temporal cortices, respectively [1].

With respect to CP classification, spastic diplegia was associated with the thalamus, temporal cortices, cerebellum, basal ganglia, and extratemporal cortices hypoperfusion. Spastic quadriplegia demonstrated a similar pattern, although the extratemporal site involved more than diplegia, and the incidence of temporal cortices hypoperfusion was reported to be lower. The basal ganglia and thalamus were commonly involved in the choreathethoid type [1].

Similarly, a study by Kerrigan et al. showed that thalamic hypoperfusion and hypometabolism are important manifestations in CP. The study reported thalamic hypometabolism in 2 of 4 patients with spastic diplegia, 6 of 7 with infantile hemiparesis, and 5 of 5 with choreoathetoid types [3].

Kerrigan et al.'s PET study showed metabolism abnormalities in CP patients [3] and revealed severe and diffuse abnormal cerebral glucose utilization concomitant with small, scattered remnants of cortical and subcortical activity in patients with spastic quadriplegia and bilateral multicystic encephalomalacia in structural imaging. In the spastic diplegia group, common abnormalities included unilateral parieto-occipital hypometabolism. The study showed decreased glucose utilization in the lenticular nucleus and thalamus in choreoathetoid types [3].

Some degree of discrepancy in the results of this study may originate from the study method (the type of functional imaging study and case selection), as well as the cause of the CP (all our patients had a history of perinatal asphyxia).

Cerebral hypoperfusion in CP originated from several mechanisms. Neuronal loss seemed to be a main cause of decreased cerebral perfusion. Even without the detection of obvious brain lesions in structural imaging, it is possible for significant hypoperfusion to occur. Brain SPECT is considered to be a functional imaging that has the capability to reveal the area of hypoperfusion following neuronal loss, whereas MRI is able to detect irreversible damage to tissue with cerebral blood flow lower than 10 ml/100 g of tissue/1 min [1]. Another reason for the inconsistency is the effect of thalamic lesions on the perfusion of other regions of the brain, which is defined as classical thalamocortical diaschisis [7]. Thalamic damage is a common finding in hypoxic brain damage, as demonstrated by Eken et al. [8]. The typical thalamocortical diaschisis is decreased metabolism or perfusion of the corresponding cerebral cortex following unilateral thalamic lesion, and retrograde thalamocortical diaschisis is decreased metabolism or blood flow in the ipsilateral thalamus, associated with the infarcted cerebral cortex [7]. Therefore, pathologies that commonly occur in CP, such as white matter lesions or PVL, could interrupt the cortico-thalamic connection, resulting in thalamic hypoperfusion by diachisis .

Hyperbaric oxygen therapy has been used to treat children with CP. The rationale for this treatment is improved oxygenation of the brain's damaged tissue [9]. At the cellular level, hyperbaric oxygen therapy seems to ameliorate neuronal and glia cells mitochondrial function and, eventually, cellular metabolism; it also appears to reduce oxidative stress, augment neurotrophins and nitric oxide concentration, and up-regulate axon guidance agents. The treatment may also induce neurogenesis and reduce apoptosis [10]. Another possible mechanism is hyperoxia's action as a neuronal stimulant [11]. Hyperoxia decreased membrane conductance and effect ion channels closure, presumably decreasing outward (K) and/or inward (Cl) currents, eventually causing depolarization and stimulate to fire rate [11]. All the mechanisms can promote neuronal activity.

In a randomized, controlled trial, Collet et al. [9] treated children suffering from CP with 40 sessions of either oxygen or air. Although significant improvement was seen in both groups with respect to motor parameters, differences between the groups were not significant.

Lacey et al. reported that hyperbaric oxygen therapy is not an effective treatment in young children with CP who did not have neonatal hypoxic-ischemic encephalopathy [12].

It should be pointed out that the current study has some drawbacks. One of the most important limitations is the relatively small sample size; however, it was quite homogenous in terms of the disease severity of patients. We should have used semiquantitative analysis software as a supplementary method to present the perfusion data. Furthermore, some brain perfusion studies showed improvement following O2 treatment without a substantial effect on clinical subjective and objective evaluation in the short-term follow up. Extended monitoring during a more prolonged time course should be considered in future studies.

Conclusion

This study demonstrated decreased cerebral perfusion in different types of CP patients. The study also revealed that hyperbaric oxygen therapy improved cerebral perfusion in a few CP patients. However, further well-designed studies are needed to assess these results.

Disclosure of conflict of interest

None.

Address correspondence to: Majid Assadi, The Persian Gulf Nuclear Medicine Research Center, Bushehr University of Medical Sciences, Bushehr 3631, Iran. Tel: 0098-771-2580169; Fax: 0098-771-2541828; E-mail: assadipoya@yahoo.com; asadi@bpums.ac.ir

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