Enhanced Perfusion in Eyes and Cerebral Perfusion Defects in a Patient with Fragile X Syndrome

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BALCI, T.A., CIFTCI, I., KABAKUS, N. and AYDIN, M. Enhanced Perfusion in Eyes and Cerebral Perfusion Defects in a Patient with Fragile X Syndrome. Tohoku J. Exp. Med., 2006, 210 (2), 169-173 —— Fragile X syndrome (FXS) is known as the most common form of inherited mental retardation. In our study, brain perfusion single photon emission computed tomography (SPECT) was performed in a 6 year-old boy diagnosed with FXS. Diffuse bilateral uptake of Technetium-99m hexamethyl propylene amine oxime (99mTc-HMPAO) was noted in his orbits, as well as cortical perfusion defects (hypoperfusion in the right parietal and the left temporal lobe). Ophthalmologic examination showed no pathological findings. Magnetic resonance imaging (MRI) revealed no abnormality in the orbital structures, although hypoplasia of cerebellum and vermis was visualized. Since the patient was crying during the injection, the increased blood flow or the increased metabolism of the eyes and/or ocular muscles may be responsible for this orbital finding. Alternatively, the enhanced uptake of HMPAO in the orbits may reflect the pathology associated with FXS, because patients with FXS might have visual-motor abnormalities. To the best of our knowledge, there has been no report documenting such an orbital uptake of HMPAO. Moreover, the visualization of decreased cerebral perfusion, with the normal findings of MRI, indicates that brain SPECT imaging with HMPAO is helpful for detecting brain abnormalities in children with FXS. ——— Tc-99m HMPAO; brain scintigraphy; orbital uptake; cerebral perfusion; fragile X syndrome
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The fragile X syndrome (FXS) is an X-linked disorder and considered as the most common form of familial mental retardation (Crawford et al. 2002; Rife et al. 2003). Speech problems and/or behavioral problems are often the first symptoms in affected kids. Mental retardation, autistic-like behaviors and hyperactivity are the most frequent behavioral abnormalities. Some morphological stigmata such as long face and large ears, and large testicular volume are also suggestive physical findings but not specific for the disease. Molecular lesions that occur in the patients with FXS are unstable expansions of a CGG-trinucleotide repeat, located in the first exon of the FMR1 gene (Gabus et al. 2004; Mandel and Biancalana 2004). The FMR1 gene codes for a cytoplasmic protein called FMRP, which plays role in the cascade of aberrations in neurodevelopment. FMRP is mostly detected in neurons and associated with polyribosomes, including those...
present in dendrites for synaptic maturation and function (Guerreiro et al. 1998). The loss of this specific protein leads to suboptimal structure and function in the central nervous system.

We presented 99mTc-hexamethyl propylene amine oxime (HMPAO) brain perfusion scintigraphy findings in a child with FXS. We wanted to emphasize particularly the diffuse HMPAO uptake in the orbits bilaterally in addition to cerebral hypoperfusion areas in temporal and parietal cortices.

**CASE REPORT**

A 6 year-old boy was referred to pediatrician with the complaint of hyperactivity and disobedience. Following the physical and neurological examinations and IQ tests, electroencephalography (EEG), magnetic resonance (MRI) and single photon emission computed tomography (SPECT) imaging of the brain were performed. Informed consent was obtained from the parents of the child. The child did not take any medication during the examinations. Elongated face, large ears, macroorchidism and hypospadias were noted in physical examination, and mental retardation and attention deficit hyperactivity disorder in neuropsychiatric examination. Electroencephalographic record revealed paroxysmal slow waves in the posterior areas.

After half an hour of a good intravenous line, 7 mCi of 99mTc-HMPAO (Brain-SPECT, Medi-Radiopharma Ltd., Budapest, Hungary) was injected to the child for brain SPECT study. Injection room was very quiet and dimmed; and

![SPECT image](image)

**Fig. 1.** Tc-99m HMPAO brain SPECT images. Diffuse bilateral HMPAO uptake in the orbits (arrows) and the hypoperfusion in the left temporal and right parietal lobes were observed.
the ears and eyes of the patient were open. Forty-five minutes after injection of 99mTc-HMPAO, chloral hydrate (50 mg/kg/dose) was used for sedation. SPECT images were obtained with a single-head gamma camera fitted with low-energy high-resolution parallel-hole collimator (Toshiba GCA 602A, Toshiba, Tokyo). Images were acquired almost one hour after intravenous injection of Tc-99m-HMPAO. The child was in supine position and sleeping during the acquisition, which was performed in 25 minutes with 64 x 64 matrices, 25 seconds per image and 6° steps for whole circle. Transaxial, sagittal and coronal slices parallel to orbito-meatal line were obtained. Hypoperfusion in the left temporal and the right parietal lobe were noted. Besides cortical perfusion defects, we interestingly detected diffuse bilateral orbital HMPAO uptake (Fig. 1). We learned that the child had cried although an intravenous catheter was used during injection.

MRI revealed no pathology about the orbital structures, although cerebellar and vermal hypoplasia were visualized (Fig. 2). Ophthalmologic and visual examinations were normal as well.

**DISCUSSION**

Epidemiological studies report that FXS is responsible for mental retardation in one in approximately 4,000-6,000 males of European descent (Crawford et al. 2002). The cognitive, behavioral, and physical phenotype varies by sex, with males being more severely affected because of the X-linked inheritance of the mutation. The risk of developing the disease appears to increase in sequential generations of the family through maternal transmission. Thus, reliable tests for early diagnosis and genetic counseling have to be established for the favor of future generations. Physical and neuropsychiatric examination findings in the patient were in concordance with the literature (Guerreiro et al. 1998; Artigas-Pallares and Brun-Gasca 2004). EEG findings were abnormal as well. Although MRI did not reveal any cerebral structural pathology, hypoplasia of the cerebellum and vermis were identified. Cerebellar and vermal hypoplasia have been reported for this disease as the most common abnormality determined by MRI studies (Hessl et al. 2004). This abnormality was suggested to be responsible for behavioral abnormalities in FXS, including hyperactivity and attention deficits.

On the SPECT studies of the FXS patients, brain perfusion abnormalities have been observed in rather wide areas (frontal, parietal and even cerebellar areas). Guerreiro and colleagues (1998) reported hypoperfusion in the inferior of the frontal lobes as the most frequent finding. In an FDG-PET study, it has been reported that regional glucose metabolism of the brain is also affected in adult patients with FXS showing asymmetry in metabolism of the superior parietal lobe (Schapiro et al. 1995). In our patient, SPECT images
revealed decreased perfusion of the right parietal and left temporal areas compared with opposite hemisphere. Hypoperfusion in the left temporal lobe of our patient was especially a different finding which was not found in the literature. The reduction in cerebral perfusion may be related to functional disturbance in brains of children with FXS. In addition, we want to particularly emphasize that diffuse bilateral HMPAO uptake has been noted in the orbits of the patient. There are many reports about oculo-visual dysfunctions in FXS, including chorioretinal lesion, strabismus, refractive amblyopia, anisometropia etc (Amin and Maino 1995). Thus, we can suppose that this uptake might be an initial finding of a subsequent pathology relevant with FXS, although the child did not have any abnormality at present in ophthalmologic examination and MRI. We planned to follow our patient for a possible pathology relevant with such uptake.

In brain SPECT study, HMPAO uptake out of the central nervous system is an unusual finding except for the physiological uptake in the nasal area (hot nose). 99mTc-HMPAO rapidly disappeared from the blood after intravenous administration. Uptake in the brain reaches the maximum level within a few minutes after injection. The cerebral activity rapidly washes out of the brain after which there is little loss of activity for the following 24 hrs. The activity, which is not associated with the brain, is widely distributed throughout the body, particularly in muscle and soft tissue. Over the 48 hrs after injection, most of the injected dose is excreted through the urine and the gut. It was found that the highest doses occur at the lacrimal glands, gallbladder and kidneys (Soundy et al. 1990). However they reported 99mTc-HMPAO uptake in lacrimal glands in only 6 of the 26 volunteer patients. In the majority of subjects there was no uptake in the lacrimal gland. Calculation of lacrimal gland dosimetry in the brain-imaging using 99mTc-HMPAO demonstrated that only 11% of the patients showed lacrimal gland uptake (Villanueva-Meyer et al. 1990). Capa et al. (2000) reported bilateral increased TI-201 uptake in the lacrimal glands of a crying child during injection. They suggested that the uptake was related to the increased blood flow in the glands. The same mechanism might be responsible for the symmetrical HMPAO uptake in the eyes of our patient because of the same reason, i.e., crying of the child. However, although we had some patients who were crying during injection, we did not previously observe such an uptake. Furthermore, the uptake of our patient seems to be just in the eye spheres instead of the lachrymal glands. Mitochondria are a major subcellular fraction for the uptake of 99mTc-HMPAO (Fujibayashi et al. 1998). Taking account of this intracellular accumulation of the 99mTc-HMPAO, we could speculate that the increased metabolism of the eyes and/or eye muscles during crying could be another reason for the radionuclide accumulation.

In conclusion, to the best of our knowledge, this patient is a very demonstrative and unique case showing an orbital HMPAO uptake. Moreover, visualization of decreased perfusion areas indicates that HMPAO brain SPECT is sensitive for detecting brain abnormalities in children with FXS, even when MRI shows no abnormality in these areas.

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References


