Visualization of Interscapular Brown Adipose Tissue Using ^{99m}Tc-Tetrofosmin in Pediatric Patients

Kazuki Fukuchi, MD[1]; Yasuo Ono, MD[2]; Yayoi Nakahata, MD[2]; Yoko Okada, MD[2]; Kohei Hayashida, MD[1]; and Yoshio Ishida, MD[1]

[1]Department of Radiology, National Cardiovascular Center, Suita, Osaka, Japan; and [2]Department of Pediatrics, National Cardiovascular Center, Suita, Osaka, Japan

Brown adipose tissue (BAT) is a site of nonshivering thermogenesis in mammals. The mitochondria of BAT operate in an uncoupled mode and increase fatty acid oxidation to produce heat at birth. Thus, the BAT of human infants and children contains more active mitochondria than that of adults. We surmised that because ^{99m}Tc-tetrofosmin can be absorbed by functional mitochondria in the myocardium and in tumor cells, it could reveal mitochondrial function in BAT. **Methods:** Between January 1999 and December 2002, we retrospectively analyzed 385 consecutive studies of ^{99m}Tc-tetrofosmin uptake in pediatric patients with cardiac disorders. All patients with symmetric ^{99m}Tc-tetrofosmin accumulation within the neck and shoulder region according to planar images were selected, and the features of the uptake were analyzed. **Results:** Increased symmetric ^{99m}Tc-tetrofosmin uptake in the interscapular BAT was a typical profile of 65 of the 385 patients (17%). The frequency of ^{99m}Tc-tetrofosmin uptake was significantly higher in winter than in spring or summer ($P < 0.05$) and prominent in newborns. The frequency peaked between 0 and 2 y of age and then declined with age. **Conclusion:** Gamma-camera imaging with ^{99m}Tc-tetrofosmin can reveal interscapular BAT distribution in infants and children in terms of mitochondrial activity.

Key Words: ^{99m}Tc-tetrofosmin; brown adipose tissue; pediatrics

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Brown adipose tissue (BAT) is a thermogenic organ that plays an important role in the energy balance. BAT is located mainly in the deep cervical region and at the interscapular site (*1,2*). In contrast to other cells, including white adipocytes, BAT expresses mitochondrial uncoupling protein, which allows the mitochondria to uncouple oxidative phosphorylation and use substrates (*3*). BAT is of particular importance to neonates, small mammals in cold environments, and animals that hibernate, because it can dissipate stored energy as heat (*4,5*). Therefore, the mitochondrial function in BAT of human infants and children might be more active than that of adults.

Recently, interscapular BAT has been visualized as enhanced uptake in the neck and shoulder by ^{123}I-metaiodobenzylguanidine (MIBG) and ^{18}F-FDG PET (*6–8*). Such tracer uptake might represent BAT metabolic activity that is stimulated by the sympathetic nervous system under physiologic conditions. We therefore postulated that mitochondrial function could be revealed in BAT by gamma-camera imaging using ^{99m}Tc-tetrofosmin because it is taken mainly into myocytes and tumor cells, depending on their mitochondrial activity (*9,10*).

The aim of this study was to determine whether ^{99m}Tc-tetrofosmin accumulates in the interscapular BAT of children and, if so, to define details of the mechanism.

MATERIALS AND METHODS

We retrospectively studied 385 ^{99m}Tc-tetrofosmin scintigrams from 329 consecutive pediatric patients between January 1999 and December 2002 at our institution. All ^{99m}Tc-tetrofosmin scans were routinely obtained for cardiac reasons after the parents gave informed consent. The group consisted of 185 male patients and 144 female patients with a mean age of 9.1 ± 6.1 y (age range, 0–19 y). All patients lived in a temperate climate in the northern hemisphere within a 2° difference in latitude.

A weight-adjusted dose of ^{99m}Tc-tetrofosmin (Nihon Medi-Physics Co.) calculated with reference to the recommendations of the European Association of Nuclear Medicine (*11*) was injected into a peripheral vein in all children. Forty-five minutes later, anterior planar scans including the neck and chest were acquired for 150 s using a gamma-camera system (Vertex; ADAC Laboratories) equipped with a low-energy, general-purpose collimator. The image acquisition parameters were a 256 × 256 matrix and a 20% main window centered on the ^{99m}Tc-photopeak energy (140 keV). Patients were sedated when necessary. All studies were considered technically adequate.

Two experienced nuclear medicine physicians independently read all studies. Using examples of the location of interscapular BAT by ^{123}I-MIBG and ^{18}F-FDG (*6–8*), the results were considered positive if the amount of symmetric uptake was more than

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For correspondence or reprints contact: Kazuki Fukuchi, MD, Department of Radiology, National Cardiovascular Center, Fujishiro-Dai 5-7-1, Suita, Osaka, 565-8565 Japan.

E-mail: kfukuchi@hsp.ncvc.go.jp

that of the surrounding tissues within the neck and shoulder. If the interpretations of the observers disagreed, a consensus was used for analysis.

All patients with positive findings were selected and their characteristics were analyzed, especially with respect to sex, age, and seasonality of uptake. To analyze seasonal differences, 4 periods of 3 mo each were defined as winter (December, January, February), spring (March, April, May), summer (June, July, August), and fall (September, October, November).

The interobserver agreement of image interpretation was estimated using the κ statistic (*12*). The concordance was considered to be good for κ values more than 0.6, moderate for values from 0.6 to 0.4, and poor for values less than 0.4 (*13*). The χ^2 test for independence analyzed differences in the frequency of positive findings between seasons and sex. Probability values less than 0.05 were considered significant.

RESULTS

All images were considered appropriate for interpretation. Interobserver agreement on positive observations was 0.96, and the κ value was 0.86. Symmetric ^{99m}Tc-tetrofosmin uptake in the neck and shoulder region was typically increased in 65 of the 385 studies (17%). Twenty-eight of these 65 studies were of female patients (43%), and 37 were of male patients (57%). The sex of the patient did not appear to be a related factor. The patient diagnoses were congenital heart anomaly (n = 39), idiopathic dilated cardiomyopathy (n = 6), Kawasaki disease (n = 3), hypertrophic cardiomyopathy (n = 3), Bland–White–Garland syndrome (n = 3), and other miscellaneous, rare cardiac disorders (n = 11). No relationship between disease and ^{99m}Tc-tetrofosmin uptake was apparent in these patients. Representative positive images from patients of various ages showed apparently symmetric ^{99m}Tc-tetrofosmin accumulation in the neck and shoulders (Fig. 1).

Figure 2 shows the number of patients and the frequency of ^{99m}Tc-tetrofosmin accumulation at various ages from neonate to teenager. However, the frequency tended to be higher in the newborn to 2-y-old age group and declined with age. Figure 3 shows the seasonality of positive ^{99m}Tc-tetrofosmin uptake. Although the results were positive during all 4 seasons, the frequency was significantly higher in winter (29%) than in spring (16%) or summer (9%) ($P <$ 0.05, respectively). Figure 4 shows serial ^{99m}Tc-tetrofosmin images from the same patient during different seasons. Interscapular BAT accumulated ^{99m}Tc-tetrofosmin during the winter but not during the warmer season.

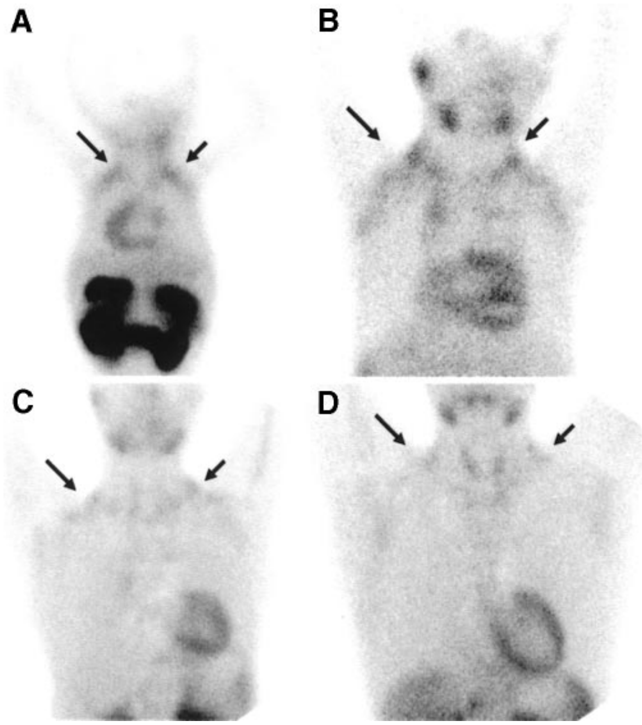

FIGURE 1. Representative images of ^{99m}Tc-tetrofosmin uptake in neck and shoulder of patients of various ages: anterior planar images of upper body from 6-wk-old boy with dextrocardia (A), 6-y-old boy with double-outlet right ventricle (B), 14-y-old boy with ventricular septal defect (C), and 19-y-old man with Kawasaki disease (D). Arrows indicate symmetric ^{99m}Tc-tetrofosmin uptake in shoulder.

DISCUSSION

Our study revealed that ^{99m}Tc-tetrofosmin uptake in the interscapular BAT can be identified in pediatric patients. In fact, we have already described an infant with bilateral shoulder uptake of ^{99m}Tc-tetrofosmin (*14*). Other authors have also reported a similar type of ^{123}I-MIBG or ^{67}Ga-citrate distribution (*15–18*). However, they and we supposed that such accumulation was in the pleural apex or in skeletal muscle, and the reason for such uptake remained obscure. Okuyama et al. recently reported that bilateral shoulder ^{123}I-MIBG uptake involves BAT, which is regulated by the sympathetic nervous system (*6*). Moreover, coregistered PET/CT technology has revealed that ^{18}F-FDG uptake is increased in BAT of the cervical and thoracic spine region (*7,8*). The ^{99m}Tc-tetrofosmin uptake identified in the present study is consistent with these findings of interscapular BAT from the viewpoint of the site of tracer accumulation. To our knowledge, this is the first report to describe ^{99m}Tc-tetrofosmin uptake in the interscapular BAT regions of a reasonable size of patient cohort.

Interscapular BAT uptake of ^{99m}Tc-tetrofosmin can be explained in 2 ways. First, the thermogenic activity of BAT requires a very high perfusion rate through its vascular system to supply both oxygen and substrate to the mitochondria (*5*). Therefore, ^{99m}Tc-tetrofosmin accumulation can represent abundant blood flow in BAT. Second, BAT has numerous, ultrastructurally large mitochondria packed with cristae and containing thermogenic uncoupling protein. Myocytes and tumor cells accumulate ^{99m}Tc-tetrofosmin depending on their mitochondrial activities and density (*9,10*). Consequently, ^{99m}Tc-tetrofosmin might explain not only tissue perfusion but also mitochondrial density and function when BAT is activated.

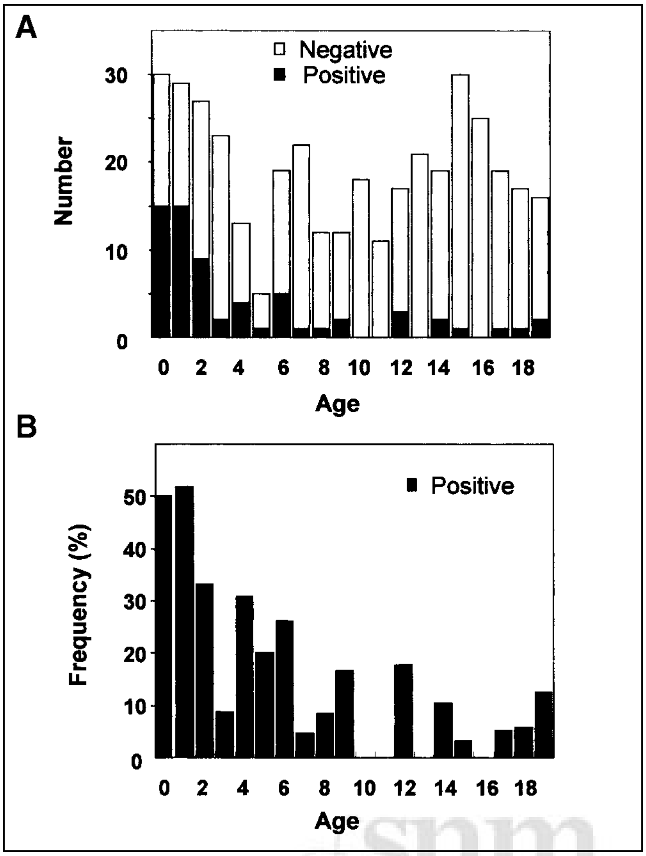

FIGURE 2. Relationship between frequency of ^{99m}Tc-tetrofosmin uptake in interscapular BAT and age (years): number of studies (A) and frequency (B).

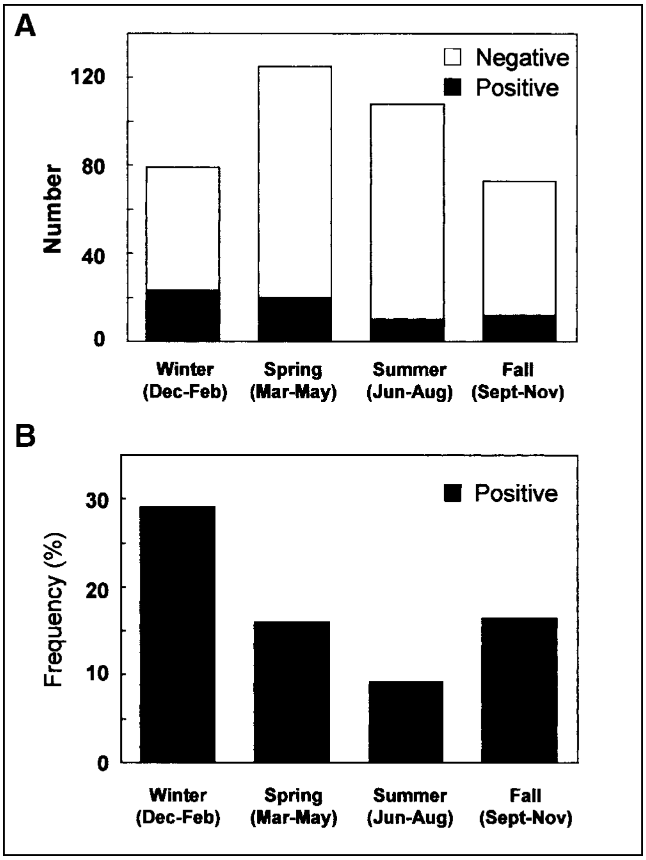

FIGURE 3. Relationship between frequency of ^{99m}Tc-tetrofosmin uptake in interscapular BAT and season: number of studies (A) and rate of BAT uptake (B) during different seasons. Frequency is significantly greater in winter than in spring or summer.

The present study found that age and season were factors that tended to influence ^{99m}Tc-tetrofosmin uptake. At birth, BAT plays an important role in response to cold exposure and maintains the body temperature (*3*). Nonshivering thermogenesis is the principal mechanism of neonatal heat generation because skeletal muscle function is not fully developed. Some investigators have identified significant amounts of BAT in prenatal and neonatal humans (*19*,*20*). Its function decreases with age as the mechanism of thermogenesis changes from BAT to shivering muscle. The present study found that ^{99m}Tc-tetrofosmin uptake in the shoulder and neck region of neonates and infants declined with age. This finding is consistent with the features of age-related BAT thermogenesis. On the other hand, cold exposure is a physiologic stimulus that activates the sympathetic nervous system to induce both the mass and the metabolic activity of BAT, which leads to an increased capacity for nonshivering thermogenesis (*21*,*22*). Rafael et al. reported that the amount of BAT mitochondrial protein is increased by a factor of 2.6 during acclimatization from summer/indoor to winter/outdoor conditions in the Djungarian hamster (*23*). Gene expression for uncoupling proteins is more abundant in the BAT of animals reared at 18°C than at 30°C (*24*). The seasonal adaptation of BAT is the same in outdoor workers (*25*). Our finding that ^{99m}Tc-tetrofosmin uptake is prominent during the winter is consistent with these reports.

The present study found that ^{99m}Tc-tetrofosmin uptake in the interscapular BAT was increased in 17% of patients. This rate is greater than the findings of BAT imaging studies using ^{123}I-MIBG (10%) or ^{18}F-FDG (2.5%–4.0%) (*6*–*8*). The population and patient characteristics differ between

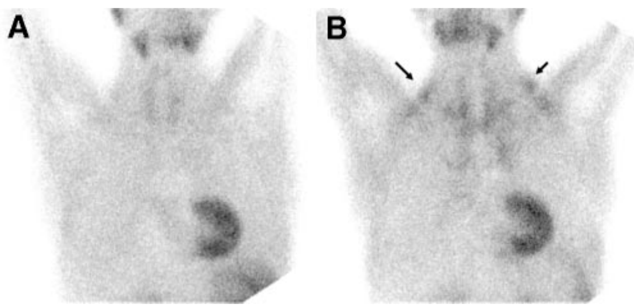

FIGURE 4. Serial ^{99m}Tc-tetrofosmin images of same patient at different seasons: images acquired in April 2002 (A) and December 2002 (B). Arrows indicate typical ^{99m}Tc-tetrofosmin uptake in interscapular BAT.

our study and these. Santos et al. reported that cardiovascular disease was the most common type of illness in adult patients with BAT accumulation (*26*). Because all our patients had various types of heart disease, the frequency of interscapular BAT visualization by ^{99m}Tc-tetrofosmin might be relatively greater than that of other studies.

We did not discover a direct link between the shoulder uptake of ^{99m}Tc-tetrofosmin and actual interscapular BAT activity. Ethical reasons and the fact that we performed a retrospective study prevented us from obtaining biopsy specimens. Nevertheless, none of these patients had bony or soft-tissue abnormalities that were clinically or radiographically detectable in the neck and shoulder. Moreover, the age dependence and seasonal frequency of ^{99m}Tc-tetrofosmin uptake indicated that the accumulation reflects the metabolic activity of interscapular BAT.

In routine clinical practice, physicians should be aware of this phenomenon. Although ^{99m}Tc-tetrofosmin can be taken up by tumor or lymph nodes, interscapular ^{99m}Tc-tetrofosmin uptake should be recognized as BAT and not be interpreted as pathologic. Moreover, BAT has become a recent focus in terms of obesity rather than thermogenesis, because type of obesity and BAT activity are related (*27*). The mechanism of obesity and its relationship to BAT function could be noninvasively examined using ^{99m}Tc-tetrofosmin scintigraphy. Further studies are necessary to establish the significance of ^{99m}Tc-tetrofosmin scintigraphy in BAT imaging.

CONCLUSION

Our results indicate that symmetric ^{99m}Tc-tetrofosmin uptake in the shoulder region of infants and children is related to the amount and function of interscapular BAT. In addition, ^{99m}Tc-tetrofosmin scintigraphy can image human BAT distribution in terms of mitochondrial activity.

REFERENCES

1. Johansson B. Brown fat: a review. *Metabolism.* 1959;8:221–240.
2. Lean MJ, Trayhurn P. Brown adipose tissue in humans. *J Obes Weight Regulation.* 1987;6:234–253.
3. Nicholls DG. A history of UCP1. *Biochem Soc Trans.* 2001;29:751–755.
4. Hatai S. On the presence in human embryos of an interscapular gland corresponding to the so-called hibernating gland of lower mammals. *Anat Anz.* 1902;21:369–373.
5. Rothwell NJ, Stock MJ. A role for brown adipose tissue in diet-induced thermogenesis. *Nature.* 1979;281:31–35.
6. Okuyama C, Sakane N, Yoshida T, et al. ^{123}I- or ^{125}I-metaiodobenzylguanidine visualization of brown adipose tissue. *J Nucl Med.* 2002;43:1234–1240.
7. Hany TF, Gharehpapagh E, Kamel EM, Buck A, Himms-Hagen J, Von Schulthess GK. Brown adipose tissue: a factor to consider in symmetrical tracer uptake in the neck and upper chest region. *Eur J Nucl Med Mol Imaging.* 2002;29:1393–1398.
8. Cohade C, Osman M, Pannu HK, Wahl RL. Uptake in supraclavicular area fat ("USA-Fat"): description on ^{18}F-FDG PET/CT. *J Nucl Med.* 2003;44:170–176.
9. Younès A, Songadele JA, Maublant J, Platts E, Pickett R, Veyre A. Mechanism of uptake of technetium-tetrofosmin. II: Uptake into isolated adult rat heart mitochondria. *J Nucl Cardiol.* 1995;2:327–333.
10. Bernard BF, Krenning EP, Breeman WA, et al. ^{99m}Tc-MIBI, ^{99m}Tc-tetrofosmin and ^{99m}Tc-Q12 in vitro and in vivo. *Nucl Med Biol.* 1998;25:233–240.
11. Piepsz A, Hahn K, Roca I, et al. A radiopharmaceuticals schedule for imaging in paediatrics. Paediatric Task Group European Association Nuclear Medicine. *Eur J Nucl Med.* 1990;17:127–129.
12. Gjorup T, Brahm M, Fogh J, Munck O, Jensen AM. Interobserver variation in the detection of metastases on liver scans. *Gastroenterology.* 1986;90:166–172.
13. Fukuchi K, Katafuchi T, Fukushima K, et al. Estimation of myocardial perfusion and viability using simultaneous ^{99m}Tc-tetrofosmin–FDG collimated SPECT. *J Nucl Med.* 2000;41:1318–1323.
14. Fukuchi K, Ono Y, Ishikawa Y, Okada Y, Hayashida K, Ishida Y. Harness-shaped distribution in pediatric Tc-99m tetrofosmin scintigraphy. *Clin Nucl Med.* 2002;27:303.
15. Bonnin F, Lumbroso J, Tenenbaum F, Hartmann O, Parmentier C. Refining interpretation of MIBG scans in children. *J Nucl Med.* 1994;35:803–810.
16. Lumbroso J, Giammarile F, Hartmann O, Bonnin F, Parmentier C. Upper clavicular and cardiac meta-[^{123}I]iodobenzylguanidine uptake in children. *Q J Nucl Med.* 1995;39:17–20.
17. Elgazzar H, Gelfand MJ, Washburn LC, et al. I-123 MIBG scintigraphy in adults: a report of clinical experience. *Clin Nucl Med.* 1995;20:147–152.
18. Lewis GW, Mansberg R, Howman-Giles R. A "harness" distribution pattern on pediatric Ga-67 scintigraphy. *Clin Nucl Med.* 1999;24:527–528.
19. Aherne W, Hull D. Brown adipose tissue and heat production in the newborn infant. *J Pathol Bacteriol.* 1966;91:223–234.
20. Itoh S, Kuroshima A. Distribution of brown adipose tissue in Japanese newborn infants. *J Physiol Soc Jpn.* 1967;29:660–661.
21. Bukowiecki L, Collet AJ, Follea N, Guay G, Jahjah L. Brown adipose tissue hyperplasia: a fundamental mechanism of adaptation to cold and hyperphagia. *Am J Physiol.* 1982;242:E353–E359.
22. Harri M, Dannenberg T, Oksanen-Rossi R, Hohtola E, Sundin U. Related and unrelated changes in response to exercise and cold in rats: a reevaluation. *J Appl Physiol.* 1984;57:1489–1497.
23. Rafael J, Vsiansky P, Heldmaier G. Seasonal adaptation of brown adipose tissue in the Djungarian hamster. *J Comp Physiol.* 1985;155:521–528.
24. Young JB, Weiss J, Boufath N. Effects of rearing temperature on sympathoadrenal activity in young adult rats. *Am J Physiol Regul Integr Comp Physiol.* 2002;283:R1198–R1209.
25. Huttunen P, Hirvonen J, Kinnula V. The occurrence of brown adipose tissue in outdoor workers. *Eur J Appl Physiol Occup Physiol.* 1981;46:339–345.
26. Santos GC, Araujo MR, Silveira TC, Soares FA. Accumulation of brown adipose tissue and nutritional status: a prospective study of 366 consecutive autopsies. *Arch Pathol Lab Med.* 1992;116:1152–1154.
27. Clement K, Ruiz J, Cassard-Doulcier AM, et al. Additive effect of A–>G (-3826) variant of the uncoupling protein gene and the Trp64Arg mutation of the β3-adrenergic receptor gene on weight gain in morbid obesity. *Int J Obes.* 1996;20:1062–1066.