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Case control study of cerebral perfusion deficits in divers using $^{99}Tc^{m}$ hexamethylpropylene amine oxime

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Hodgson M, Smith DJ, MacLeod MA, Houston AS, Francis TJR. Case control study of cerebral perfusion deficits in divers using $^{99}Tc^{m}$ hexamethylpropylene amine oxime. Undersea Biomed Res 1991; 18(5–6):421–431.—In a preliminary report, Adkisson et al. (*Lancet* 1989; 2:119–121) used $^{99}Tc^{m}$-hexamethylpropylene amine oxime (HMPAO) single photon emission computed tomography (SPECT) to provide evidence for cerebral perfusion deficits in 28 cases of dysbarism. The report caused concern because these deficits were found even in cases in which the clinical manifestations were limited to the spinal cord. To address this issue further, a case-control study of cerebral perfusion using $^{99}Tc^{m}$-HMPAO SPECT is reported. Four groups of 10 subjects were studied: a) divers scanned on average 11 days after treatment of neurologic decompression illness, b) divers scanned 3–5 yr after treatment for neurologic decompression illness, c) diver controls, and d) population controls. All groups were matched for age, and the divers were further matched for general diving experience. The scans were randomized and reported blind to history. Despite a trend toward larger numbers of deficits in individuals with decompression illness, the 4 groups were statistically indistinguishable. Furthermore, no correlation was found between the location of the perfusion deficits and the clinical presentation. These results indicate that $^{99}Tc^{m}$-HMPAO SPECT scanning requires further evaluation before clinical significance can be ascribed to perfusion deficits found in divers.

$^{99}Tc^{m}$ hexamethylpropylene amine oxime (HMPAO)
single photon emission computed tomography (SPECT)
cerebral
perfusion
dysbarism
decompression sickness
decompression illness
diving

Questions of occult neurologic injury resulting from diving, with or without a history of decompression illness, have been posed by various authors (1–7). Postmortem studies have reported lesions in the spinal cord after clinical recovery from decompression sickness (DCS) (8) and more recently abnormalities have been found in the brains of divers, many of whom had not reported a history of decompression illness (9). Because of these findings, there is concern that divers may be suffering long-term neurologic damage.

Various imaging methods have been employed to attempt to provide evidence for these suspicions. Polkinghorne et al. (6) reported a study using retinal fluorescein angiography in 84 divers, 12 of whom had a previous history of decompression sickness (DCS). They found low retinal capillary densities at the fovea, microaneurysms, small areas of capillary nonperfusion, and increased abnormalities of the retinal pigment epithelium. The extent of the abnormalities was related to the length of the diving history rather than to decompression illness (DCI). No subject had any demonstrable visual loss. Since the retina is generally felt to be a "window" into the central nervous system, the authors suggested that their findings may imply that asymptomatic central nervous system injury occurs as a result of diving.

Most imaging techniques have not demonstrated lesions within the brain following DCI except in the most severely affected. Computed tomography (CT) scans have shown small, low-density areas in serious cases of dysbaric illness (10), but have not detected abnormalities in the majority (11). Nuclear magnetic resonance imaging (MRI) should be capable of detecting more subtle changes that may be associated with DCI—such as micro-embolic damage and possibly in situ gas bubble formation in tissues. Warren et al. (12) reported 14 cases of "barotrauma" which were investigated with MRI and CT. Three out of 4 patients with symptoms and signs suggestive of intracranial injury demonstrated abnormalities on MRI, and 1 had a positive scan. Three out of 12 patients with "spinal cord symptoms" had abnormal MRI scans of their spinal cord. Four of 12 patients had cerebral deficits demonstrated by MRI, 2 of these had clinical manifestations referable to the cerebrum. Todnem et al. (13) reported a cross-sectional MRI study of 105 divers and 49 controls. Although 51% of the divers had a history of DCS, no significant difference was found between the 2 groups with respect to the number of abnormalities found at MRI.

In 1989, Adkisson et al. (1) reported the results of $^{99}Tc^{m}$-labeled hexamethylpropylene amine oxime [$^{99}Tc^{m}$-HMPAO single photon emission computerized tomography (SPECT)] scanning performed on 28 cases of dysbaric illness. Cerebral perfusion deficits were reported in all of the cases of neurologic DCI. Such deficits were not unexpected in classic cases of cerebral arterial gas embolism; however, it was surprising that deficits were found so consistently in cases of DCS and particularly in cases with paraplegia due to presumed spinal cord disease. Criticisms of this pilot study included the absence of a control population, incompletely blinded interpretation of the scans, and the absence of premorbid scans. These investigators went on to report a small follow-up pilot series of 18 patients who were rescanned at varying intervals. The majority of patients were found to have persistent deficits (14). A larger follow-up study of 27 divers supported the conclusion that perfusion deficits seem to persist in the majority of cases (15).

The potential significance and persistence of cerebral perfusion deficits identified with $^{99}Tc^{m}$-HMPAO SPECT is particularly important in relation to advice on future employment and the design of medical screening for divers. The primary objective of this study was therefore to corroborate the conclusions of previous studies using a more rigorous study design. Additionally, the study was designed to explore whether divers with no history of DCI have perfusion deficits that can be detected using $^{99}Tc^{m}$-HMPAO SPECT and whether such deficits can be demonstrated in individuals 3–5 yr after their initial treatment for DCI.

MATERIALS AND METHOD

Subject selection

Four groups of 10 age-matched subjects were scanned using $^{99}Tc^{m}$-HMPAO SPECT. The 4 groups were: a) divers scanned on average within 11.3 days (range 1–45 days) of treatment for neurologic DCI (new cases), b) divers scanned 3–5 yr after treatment for neurologic DCI (old cases), c) diver controls, and d) population controls. All groups were matched for age.

Exclusion criteria

The complete range of conditions that are associated with cerebral perfusion deficits detected by $^{99}Tc^{m}$-HMPAO SPECT is not known. Exclusion criteria for this study were based on conditions either known to produce such deficits, such as cerebrovascular disease, or those in which a deficit could be readily postulated. These included history of seizures, birth trauma, unconsciousness secondary to carbon monoxide poisoning, and a history of boxing or significant head injury. A head injury was considered significant if there was a history of a skull fracture, loss of consciousness for 5 or more min, posttraumatic amnesia greater than 1 h, or significant postinjury sequelae. Females were also excluded from the study because all the cases were male.

Divers with decompression illness

Before entry into the study, all case records selected were reviewed by 3 diving medicine specialists who were unfamiliar with the cases. Only those cases in which there was concordance on the diagnosis of neurologic DCI were admitted to the study.

Old cases: To find suitable old cases, all available records from 1981 to 1985 maintained by the Royal Navy at the Institute of Naval Medicine, Alverstoke, were scrutinized. Criteria for selection included: a) definitive evidence of DCI requiring treatment with recompression therapy, b) residence in southeast England, and c) adequate available contact information. All the records meeting these criteria were selected and 20 patients were identified and contacted by mail. The letter explained the nature of the intended study. Seventeen individuals replied. Of these, three did not wish to participate. One was a paraplegic who felt the journey would be too stressful, one was too busy at work in London to be able to come for the scan, and one provided no reason. Three volunteers had to be excluded because of previous skull fractures, and the remaining 11 (all male, aged 27–55) attended for a scan. One of the 11 cases (55 yr old) was later excluded because no adequate matches could be found.

New cases: New cases were randomly selected from a pool of previously scanned subjects who met the entrance criteria and who were age-matched with the old cases.

Diver controls

Two Royal Navy Sports Scuba clubs were circulated with information on the nature of the intended study and given a phone number to contact for those interested

in participating. The standard exclusion criteria plus the absence of a history of neurologic DCI were used. From the volunteers, 10 were selected who matched the subject group for approximate age and diving experience. Diving experience was grouped as novice (<30 dives), intermediate (30–300), and experienced (>300).

Nondiving controls

Nondiving, healthy, male volunteers who met the exclusion criteria were age-matched in the same way as the diver controls.

For each subject, a full medical history was taken, including the occupational history and, where appropriate, the diving history and details of any diving accidents and the outcome of treatment. Each person was examined clinically with particular attention to the neurologic system. A written report, including the results of the scan, was subsequently dispatched to the participant.

No payment was made for participation in the study, although reimbursement for loss of earnings and traveling expenses was offered. All participants had a full explanation of the proposed procedure and an opportunity to ask any questions before written consent was requested. The study was approved by the Royal Navy Clinical Research Subcommittee and the Naval Clinical Research Ethics Committee.

$^{99}Tc^{m}$-HMPAO SPECT technique

The Nuclear Medicine Department, RNH Haslar, has refined a clinical investigative tool for examining cerebral perfusion. The technique involves the intravenous injection of $^{99}Tc^{m}$-labeled HMPAO. This radiopharmaceutical crosses the intact blood-brain barrier with 3–8% becoming fixed immediately to glutathionine in the neuronal nuclei in the gray matter and the remainder circulates unchanged until excreted via the liver and gut. No further cerebral redistribution occurs until the HMPAO is metabolized. It has been shown that this binding is proportional to the blood flow at the time of the HMPAO injection (16–18). The cerebral distribution of the fixed radiopharmaceutical can be recorded with SPECT. The scans are interpreted as indicating the distribution of cerebral perfusion at the time of injection.

After the injection of HMPAO, SPECT was performed with a Siemens 75 ZLC orbiting gamma camera linked to a Nodecrest Micas 3 computer. The sinogram was acquired by use of 360° forward rotation, 64 projections on a 64 × 64 matrix, and 20 s acquisition time per projection. Images were reconstructed by filtered back projection with a Shepp-Logan filter. The reconstructed image, containing 32 trans-axial slices, was smoothed and presented on a 16-color scale image display. Asymmetrical defects were initially determined visually and quantified using a 3 × 3 pixel square comparison between the area containing the lesion and the contralateral (normal) side.

The scans were randomized with all identifiers removed and were then read by a consultant in nuclear medicine who had no knowledge of the subjects classification or history. Deficits were expressed as: [mean counts distribution in the deficit divided by mean counts distribution in the contralateral side] × 100. Identifiable perfusion deficits of less than 12% have not been included in the analysis because they are considered to be of no clinical significance.

Statistics

To examine differences between the groups, 2×2 χ^2 analysis with Yates' correction for continuity was used. When an expected cell value of less than five occurred, Fischer's exact test was applied. Friedman's nonparametric test was applied to the results to take advantage of the age-matched groups. Statistical significance was set at a level of $P = 0.05$. Simple comparisons were also made between the location of the perfusion deficits and the clinical presentations to examine their relationship.

RESULTS

Forty subjects were included in the analysis, 10 in each group. Age matching was controlled to within 4 yr of the subject's age at time of scan. The mean age (± standard error of the mean) of new cases was 37.5 ± 1.6, the old cases 38.2 ± 2.5, the diver controls 37.5 ± 1.9, and the nondiver controls 37.4 ± 1.9.

Tables 1–4 present the results of the scans. In both the new and the old cases, 8 out of 10 subjects demonstrated identifiable cerebral perfusion deficits. Seven out of 10 diver controls and 9 out of 10 nondiver controls also demonstrated identifiable deficits. Eight new cases, 6 old cases, 5 diver controls, and 5 nondiver controls demonstrated significant deficits (≥12%); 3 subjects in the old case, new case, and nondiving control groups and 1 subject from the diver control group had deficits of 18% or greater.

Our method of SPECT constructs slices that are approximately 5-mm thick. It can be postulated that a deficit that is found in more than one contiguous slice may be of greater significance than those in only one slice. Tables 1–4 present the results of an analysis of deficits that appeared in more than one contiguous slice. Again, a trend appears, with old or new case groups generally having a larger number of such deficits

TABLE 1
NEW CASES

Max. % Lesion	No. of Slices	No. of Deficits Seen in ≥2 Slices	No. of Deficits ≥12%	No. of Deficits ≥15%	No. of Deficits ≥18%
17	1	0	2	1	0
30	6	5	9	6	5
0	0	0	0	0	0
16	4	2	2	1	0
0	0	0	0	0	0
20	5	2	5	4	3
14	2	0	2	0	0
>50	6	4	4	4	4
12	3	0	2	0	0
17	3	2	2	2	0
Totals	30	15	28	18	12

TABLE 2
OLD CASES

Max. % Lesion	No. of Slices	No. of Deficits Seen in ≥2 Slices	No. of Deficits ≥12%	No. of Deficits ≥15%	No. of Deficits ≥18%
17	2	0	4	1	0
15	4	2	5	2	0
0	0	0	0	0	0
20	5	4	2	2	1
<10	2	0	0	0	0
21	3	0	3	1	1
30	3	1	3	2	1
16	4	2	2	1	0
0	0	0	0	0	0
<10	1	0	0	0	0
Totals	24	9	19	9	3

TABLE 3
DIVER CONTROLS

Max. % Lesion	No. of Slices	No. of Deficits Seen in ≥2 Slices	No. of Deficits ≥12%	No. of Deficits ≥15%	No. of Deficits ≥18%
0	0	0	0	0	0
0	0	0	0	0	0
16	3	2	2	2	0
21	3	0	3	2	1
12	1	0	1	0	0
14	2	1	1	0	0
9	2	0	0	0	0
0	0	0	0	0	0
15	2	0	1	1	0
<10	1	0	0	0	0
Totals	14	3	8	5	1

than the controls, but the differences are not statistically significant. Friedman's nonparametric test was used to test whether the new cases, old cases, or either control group were statistically different using age-matched groups for the parameters listed in Table 1. No significant differences were found.

Tables 5 and 6 summarize the clinical location of the lesions and the location of the scan deficits. Eighteen of the 20 DCI cases showed sensory/strength symptoms or signs—11 bilateral and 7 unilateral (5 right and 2 left). A comparison is made between the side of sensory/strength symptoms and the location of the deficits in

TABLE 4
NONDIVER CONTROLS

Max. % Lesion	No. of Slices	No. of Deficits Seen in ≥2 Slices	No. of Deficits ≥12%	No. of Deficits ≥15%	No. of Deficits ≥18%
0	0	0	0	0	0
20	2	1	2	2	1
23	2	0	2	2	1
15	2	1	2	2	0
20	3	1	2	2	1
14	1	0	2	0	0
11	2	0	0	0	0
11	2	0	0	0	0
<10	1	0	0	0	0
<10	1	0	0	0	0
Totals	16	3	10	8	3

Table 7. Two patients with left-sided symptoms/signs had right-sided deficits, and 3 out of 5 of the patients with right-sided symptoms/signs had left-sided deficits. However, it can also be seen that deficits could frequently be identified on the ipsilateral side which failed to correspond with any symptom. There was no consistent correlation found between the location of deficits and the clinical presentation at the time of treatment. Five old cases had definite residual symptoms, two of which were clinically believed to be of a cerebral distribution. The side of symptoms in these 2 "cerebral" cases correlated with side-of-scan deficits. One case showed an isolated frontal lobe deficit on the scan and an alteration in this patient's affect had been noticed by his family following his diving accident.

The possibility that undetected or subtle neurologic damage is caused by dysbaric illness was also suggested by a variety of complaints from old cases returning for review. These were all subjective in patients who had otherwise achieved an apparently full recovery. The complaints most commonly described were difficulties with concentration and calculation, forgetfulness, and a feeling of mental dullness. The duration of these symptoms after recompression was variable, but usually lasted for the order of weeks. A feeling as though a haze had lifted, which coincided with a subjective return to normality, was also sometimes described.

DISCUSSION

No statistically significant difference was shown in the prevalence of cerebral perfusion deficits by $^{99}Tc^{m}$-HMPAO SPECT between individuals who had experienced DCI compared with those who had not. In contrast to previously reported findings, 6 patients with histories of neurologic DCI had no deficits, and no correlation was found between the location of the perfusion deficits and the clinical presentation.

TABLE 5
DIAGNOSIS, CLINICAL SUMMARY, AND SCAN RESULTS FOR NEW CASES

Diagnosis Acute DCI	Location	Scan Result Largest Recorded Deficit in Each Area, Number = % Deficit
Progressive, neurological, constitutional	sensation: bilateral LE—partial, fatigue, lassitude	RFP12 LFr17
Progressive, neurological	sensation: bilateral UE, LE—subjective only	RFr23 RFP17, RP14, RPP30 LFr18 LFP12, LPP20
Static, neurological, and limb pain	higher function deficit	no deficits
Progressive, neurological, and limb pain	strength: L UE sensation: L UE—subjective	RP13 LPP16
Neurological	strength: R UE sensation: L UE—subjective	no deficits
Progressive, neurological	higher function coordination	RFr20 LFP20, LP13
Neurological	sensation: R LE—partial	RPP13 LFP14
Neurological	strength: L LE sensation: bilateral LE	RFr>50 LF26 LFP22, LPP31
Progressive, neurological	strength: bilateral LE sensation: bilateral LE—total	RFP 12 LFr 12
Neurological	sensation: R UE—total over 8 × 5 cm	RFP17 LFP16

Key: LE = lower extremity, LFr = left frontal, LFP = left fronto parietal, LP = left parietal, LPP = left posterior parietal, UE = upper extremity, RFr = right frontal, RFP = right fronto parietal, RP = right parietal, RPP = right posterior parietal.

If it is assumed that cerebral perfusion deficits were present in the old cases soon after their incident, then the findings seem to suggest that these areas persist.

This study was designed to avoid some of the limitations of previous studies of divers using $^{99}Tc^{m}$-HMPAO SPECT. Diver and nondiver controls were recruited for this case-control study. It is conceivable that the controls are not representative of the normal population because they were recruited as volunteers, as is obviously required for ethical approval. Cerebral blood flow is felt to vary with age, therefore each set of cases and controls were age matched. The diagnostic classification for

TABLE 6
DIAGNOSIS, CLINICAL SUMMARY, AND SCAN RESULTS FOR OLD CASES

Diagnosis Acute DCI	Location	Scan Result Largest Recorded Deficit (≥12%) in Each Area, Number = % Deficit
Progressive, neurological	sensation: bilateral lower extremity —partial	RFP17 LFr14 LFP12, LPP12
Static, neurological, and limb pain	strength: R UE sensation: R UE—partial	RFP15, RPP14 LFr14 LFP15
Progressive, neurological	strength: bilateral LE sensation: R UE—partial	no deficits
Progressive, neurological, and limb pain	strength: bilateral LE sensation: bilateral LE—partial	RFP15 LP20
Static, neurological, and limb pain	sensation: R UE-subjective only	no deficits
Spontaneously improving, neurological	sensation: L LE—partial	RP21 LFr14 LFP30
Progressive, neurological, and audiovestibular	strength: bilateral LE	RFr15 LFr14 LFP30
Neurological	strength: bilateral UE sensation: L UE LE—partial	RFP13 LFr16
Progressive, neurological	strength: R UE LE	no deficits
Progressive, neurological	sensation: bilateral LE, UE—partial	no deficits

Key: LE = lower extremity, LFr = left frontal, LFP = left fronto parietal, LP = left parietal, LPP = left posterior parietal, UE = upper extremity, RFr = right frontal, RFP = right fronto parietal, RP = right parietal, RPP = right posterior parietal.

each case was determined independently by three diving medicine specialists. Finally, all scans were read without knowledge of the subjects history or classification by a nuclear medicine consultant (M.A.M.).

One design problem which could not be readily overcome in this study was the absence of premorbid scans. The deficits characterized as being associated with diving disease may be due to other unidentifiable causes. This problem is further exacerbated in the old cases because the scans do not have temporal proximity to

TABLE 7
MOTOR/SENSORY SYMPTOMS AND SITE OF DEFICIT (≥12%)

Side of Symptom/Sign	Site of Deficit				
	No Deficit	L Parietal	R Parietal	L frontal	R frontal
New Cases					
Left, $n = 1$	0	1	1	0	0
Right, $n = 2$	0	2	2	0	0
Bilat, $n = 5$	1	2	3	4	2
Higher, function only, $n = 2$	1	1	0	0	1
Old cases					
Left, $n = 1$	0	1	1	1	0
Right, $n = 3$	2	1	1	0	0
Bilat $n = 6$	2	3	3	3	1
Higher function only, $n = 0$	0	0	0	0	0

the accident. However, none of the subjects had reported significant interval medical histories considered potentially contributory to cerebral perfusion deficits. It is also possible that the deficits could be premorbid and therefore predispose the subjects to neurologic DCI.

There was a higher percentage of positive results in the diver and population controls than anticipated even using high (18%) percentage cutoffs. No apparent pathophysiologic explanation for these findings could be found, particularly in the light of their normal clinical examination and the careful use of exclusion criteria. Only half of the controls (10/20) were free from significant (≥12%) perfusion deficits. These findings were not expected. It is possible that asymptomatic divers sustain subtle neurologic injury as a result of their diving, but this explanation cannot pertain to the nondiver controls. Interestingly, we were unable to find other published $^{99}Tc^{m}$-HMPAO SPECT series that reported controls with which we could compare these findings.

An alternative explanation for these deficits, along with the lack of correlation between their location and clinical manifestations, is that the scan is too sensitive for this diffuse disease, thereby producing an unacceptably high false positive rate as presently analyzed. A larger population of controls is required to define the criteria for a normal scan. This is being addressed by the Nuclear Medicine Department, RNH. Furthermore, the current method of analysis only considers the number of lesions or the maximum percentage deficit; the overall volume of each deficit (presumably a better indicator of the extent of disease) is not assessed. On visual examination of the data, there seems to be a trend to more and larger deficits in the DCI groups. Volumetric analysis of the scans would be ideal; however, this is presently not available although it is also being developed.

With the small numbers involved, a clear positive/negative split of results was required to achieve statistical significance. This lack of power in the study may explain the absence of statistical significance.

In conclusion, this study supports the findings of previous studies that more cases of DCI than traditionally expected may have cerebral involvement and persistent

occult insults. Additionally, this study has demonstrated that interpretation of $^{99}Tc^{m}$-HMPAO SPECT requires further examination in relationship to diving and interpretation of normality in individuals.

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