**Key Words**

Auditory evoked magnetic fields, N100m peak latency, Mini-mental state examination, Cognitive deterioration, Interhemispheric neural conduction time

**Abstract**

Recent development of auditory-evoked magnetoencephalography (A-MEG) made it possible to measure interhemispheric neural conduction time (INCT) of auditory impulses. We estimated INCT with A-MEG and cognitive function with mini-mental state examination (MMSE) in 85 elderly patients with chronic dizziness (CD) and found that INCT was negatively correlated with MMSE scores ($p<0.001$). In 11 of 85 patients whose MMSE scores were within the normal range, A-MEG and MMSE were repeated for the subsequent 4 years to find longitudinal changes in INCT and cognitive function. The 11 patients were divided into two groups according to the baseline INCT values, such as Group A with normal INCT (n=7) and Group B with abnormally prolonged INCT (n=4). In Group A, INCT and MMSE scores remained within the normal range throughout the 4-year period. In Group B, INCT showed the tendency towards progressive prolongation during the follow-up period, and MMSE scores decreased to abnormally low levels at the third or fourth follow-up year in all the patients. The present results suggest that rapid neural interaction of both cerebral hemispheres is needed to maintain normal cognitive function. Abnormal INCT prolongation in elderly subjects suggests subclinical cortical network dysfunction and may predict the future development of cognitive deterioration.

**Introduction**

Auditory impulses originated from the unilateral ear reach the temporal auditory cortex bilaterally, although detailed neural pathways have remained unclarified. A-MEG studies have indicated that the latency of auditory-evoked neuronal action peak (N100m peak) detected at the temporal cortex ipsilateral to the auditory stimulation is always delayed as compared with that deteced at the contralateral side [Pantev, 1998]. Regarding this phenomenon, our recent A-MEG study has suggested that auditory impulses originated from the unilateral ear first arrive at the contralateral temporal cortex

and thereafter reach the ipsilateral temporal cortex through interhemispheric neural connections, thus, leading to the delay of ipsilateral N100m peak latency [Oe, 2002]. Such a conduction manner of auditory impulses enables us to measure INCT with A-MEG.

The cognitive function is operating on the basis of interactions of multiple cortical regions in both cerebral hemispheres. Provided the interacting neuronal conduction is delayed, the cognitive function may not operate smoothly. Little, however, has yet been known as to whether the time required for cortical neural interactions is related with the cognitive function.

During the last several years, we performed A-MEG and MMSE studies simultaneously in 85 elderly patients who were complaining CD. Our special interest has been focused to the cognitive function of elderly CD patients, since they commonly have white matter lesions, silent multiple infarctions and enlarged lateral ventricles on MRI [Kerber, 1998], [Starr, 2003] and since they often have depressive state [Starr, 2003] which is commonly seen in the early phase of dementia. In the present study, we studied the relationship between INCT and MMSE scores in 85 elderly patients with CD. Furthermore, in 11 of them who had normal MMSE scores at the baseline measurements, A-MEG and MMSE were yearly followed up for the subsequent 4 years to find longitudinal changes in INCT and MMSE.

**Methods**

11 normal volunteers with 52 ±15 years of age and 85 elderly patients complaining of CD with 69 ±8 years of age were subjected to the study. All the 85 patients with CD had no history of stroke or other central nervous system diseases. They visited our institute complaining of non-rotatory dizzy sensation continuing for more than 6 months. Neurological examinations showed no focal neurological abnormality, such as nystagmus, motor weakness, deep sensory impairments or limb-trunkal ataxia. All the patients underwent otorhinological examinations and auditory brain-stem response test. Those patients with auditory impairments were excluded from the study, provided the lowest

audible intensity at 1000 Hz was 30 dB or more, or the average lowest audible intensities at 125-8000 Hz were 30 dB or more in the pure tone audiogram. Furthermore, those patients with brain-stem response showing waves I, II, III, IV and V peak latencies beyond ranges 1.77±0.19, 2.83±0.15, 3.90±0.19, 5.18±0.25 and 5.77±0.31 msec, respectively, were excluded from the study. MRI (Siemens, 1.5 Tesla) performed in all the patients displayed no definitive abnormality except for white matter lesions, silent small infarctions or enlarged lateral ventricles which were observed more or less in all the patients.

A-MEG studies were performed in all the 85 patients and 11 normal volunteers using a superconducting quantum interference device system (MC-6400, Hitachi Ltd.). Detailed methods were described elsewhere [Oe, 2002]. In brief, auditory-evoked MEG study was performed as follows. Auditory stimuli with 90 dB in intensity and 1,000 Hz tone-burst were provided in the right ear, and N100m peak latency was measured at both temporal cortices. The INCT was calculated from the right and left N100m peak latencies. Cognitive function was evaluated using MMSE scores. MMSE scores from 24 to 30 were judged normal, and the scores below 24 were judged abnormally low. In 11 normal volunteers, MMSE scores were 30 exclusively, and INCT was 15.0 ± 6.1 msec. Based on this result, INCT values 2.8- 27.2 msec (mean INCT plus or minus two standard deviations of normal volunteers) were judged to indicate normal INCT range.

Following the measurements of the baseline INCT and MMSE scores, the measurements were repeated yearly in 68 CD patients who agreed with the follow-up studies. In 11 of them, both A-MEG and MMSE studies were fully performed for the subsequent 4 years. In the other 37 patients, only the second year follow-up study has been so far completed. In the remaining 20 patients, the third year follow-up study has been completed, although data of either the first year or the second year follow-up study were not available. Therefore, in the present study, only 11 patients with 4-year full studies were subjected to the analysis of longitudinal changes in INCT and MMSE scores . The 11 patients were divided into two groups according to the baseline INCT values, such as Group A with normal INCT (2.8-27.2 msec) and Group B with

abnormally prolonged INCT (more than 27.2 msec). Longitudinal changes of INCT and MMSE scores were compared between the two groups.

**Results**

In 85 elderly patients with CD, MMSE scores ranged from 18 to 30, and INCT ranged from 3.2 to 68.5 msec. MMSE scores were abnormally lowered in 12 of 85 patients showing 23 or less. In these 12 patients, silent infarcts, white matter lesions and enlargement of lateral ventricles on MRI were more remarkable as compared with those in the other 73 patients. INCT was abnormally prolonged in 22 of 85 patients showing values more than 27.2 msec. In 8 of these 22 patients, MMSE scores were abnormally lowered, while in the other 14 patients MMSE scores were within the normal range. Fig. 1 illustrates the relationship between INCT and MMSE scores in the 85 elderly patients with CD. There was a significant negative correlation between INCT and MMSE scores ($r = -0.542$, $p<0.001$).

Longitudinal changes of MMSE scores and INCT in 11 CD patients whose baseline MMSE scores were within the normal range are shown in Fig.2 (Group A) and Fig. 3 (Group B). There were 7 patients in Group A. Their mean age was 73±8 years. In Group A, the baseline INCT was 8.1±7.3 msec, and the baseline MMSE scores were 29.0±1.3. In this group, all the patients continued to show normal INCT and normal MMSE scores throughout the follow-up period except for one patient whose MMSE score decreased to 23 at the fourth follow-up year. There were 4 patients in Group B. Their mean age was 71±10 years. In Group B, the baseline INCT was 35.1 ±6.0 msec all showing abnormally longer values. However, the baseline MMSE scores were normal showing 27.4±1.1. In this group, INCT showed gradual increase with the passage of time. MMSE scores remained within the normal range in all the patients until the second follow-up year. At the third follow-up year, MMSE scores decreased to the abnormally low levels in 2 of 4 patients (22 and 23). At the fourth follow-up year, MMSE scores decreased to the abnormally low levels in all the patients showing 21.5 ±1.3. None of 11 patients in Groups A and B had noticeable episode suggesting stroke during the follow-up period. However, in all the patients of Group B, MRI

obtained in the fourth follow-up year displayed increases of silent infarcts and/or white matter lesions as compared with that obtained at the beginning of study.

**Discussion**

Previously, Pekkonen et al. reported that N100m latency in A-MEG was delayed in patients with Alzheimer's disease [Pekkonen, 1999]. In the present study, INCT was found to increase negatively correlating with MMSE scores in elderly patients with CD. The present results are compatible with those reported by Pekkonen et al.. As reported in the previous MRI stuides [Kerber, 1998], [Starr, 2003], elderly patients with CD commonly have multiple small silent infarcts, white matter lesions and enlarged lateral ventricles. Similar MRI changes were observed also in our patients with CD. MRI findings in elderly CD patients are, thus, similar to those in patients with multi-infarct dementia. MMSE scores in the baseline measurements were abnormally lowered in 12 of our 85 CD patients. Those 12 patients can be regarded multi-infarct dementia, provided abnormal MMSE score reduction indicates dementia.

In the present study, the baseline INCT was abnormally prolonged inspite of normal MMSE scores in 14 of 85 CD patients. Such a dissociation led us to perform the follow-up study. The follow-up study was perfomed in 11 patients with normal MMSE in the baseline measurements. In 4 of them whose baseline INCT was abnormally prolonged, INCT increased progressively during the follow-up period. All these 4 patients showed MMSE reduction to the abnormally low levels at the third or fourth follow-up year. Multi-infarct dementia is considered most appropriate for the diagnosis of these 4 patients judging from their MRI findings, although no stroke episode was appreciated during the follow-up period. Thus, abnormal INCT prolongation preceded 3-4 years to abnormal MMSE reduction in these patients. The cognitive function works under rapid interactions of multiple cerebral regions interconnected with neurons. The interhemispheric neuronal conduction time may be an important factor determinating the cognitive function. The degeneration or loss of interhemispheric neurons in elderly subjects may cause prolongation of INCT and may eventually bring about the deterioration of cognitive function. Longitudinal measurements of INCT with

A-MEG can be carried out easily in elderly subjects repeatedly. The measurment may be useful to predict the development of cognitive impairment in elderly subjects and may greatly contribute to the preventive medicine of dementia.

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**Figure 1.** Relationship between interhemispheric neural conduction time and mini-mental state examination scores in 85 elderly patients with chronic dizziness.

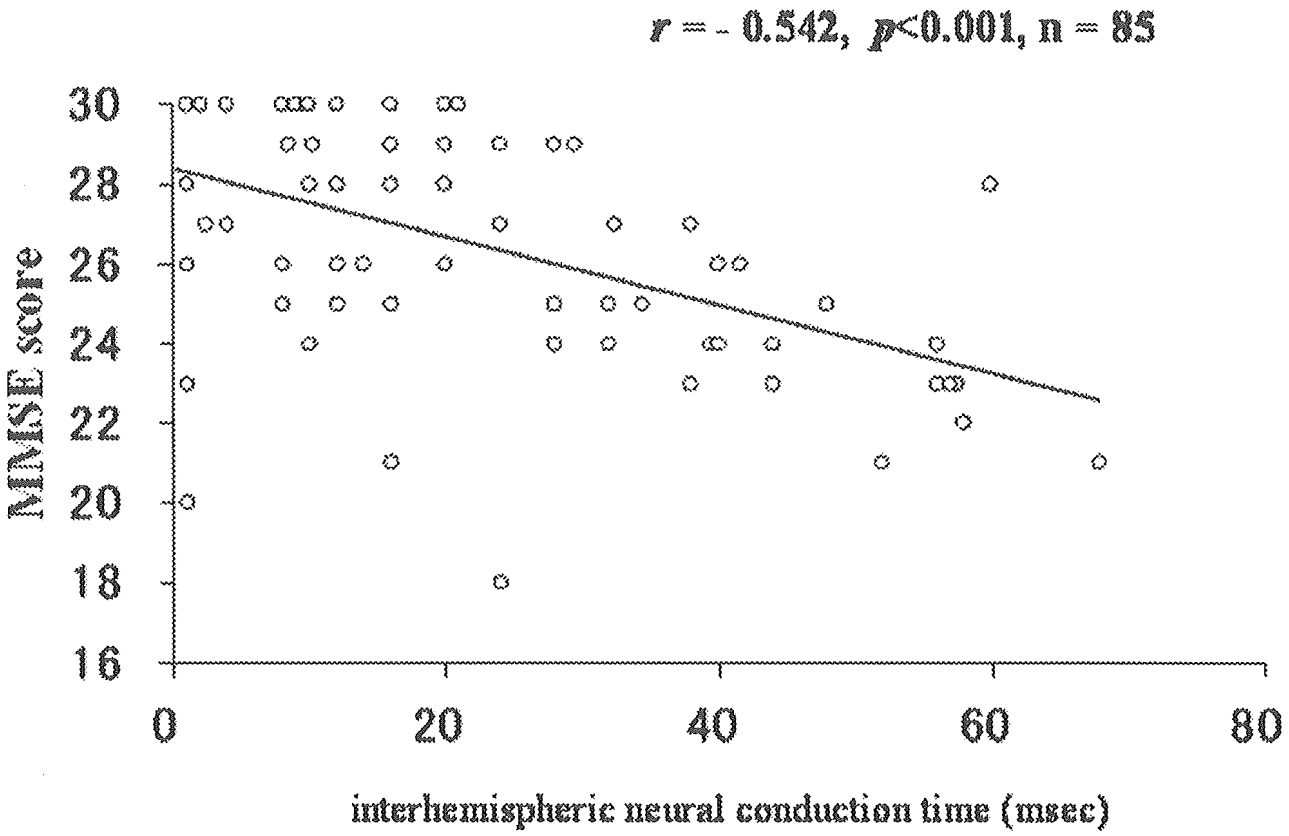


**Figure 2.** Longitudinal changes of INCT and MMSE scores in Group A

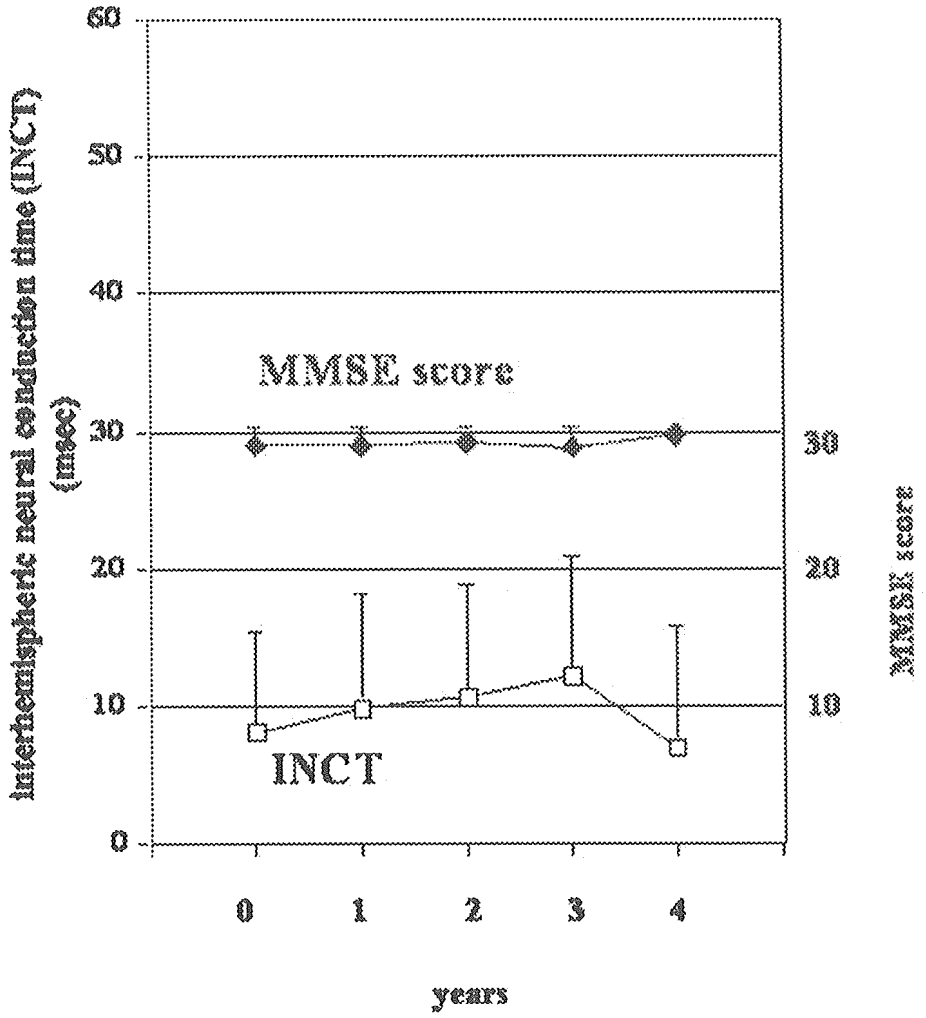
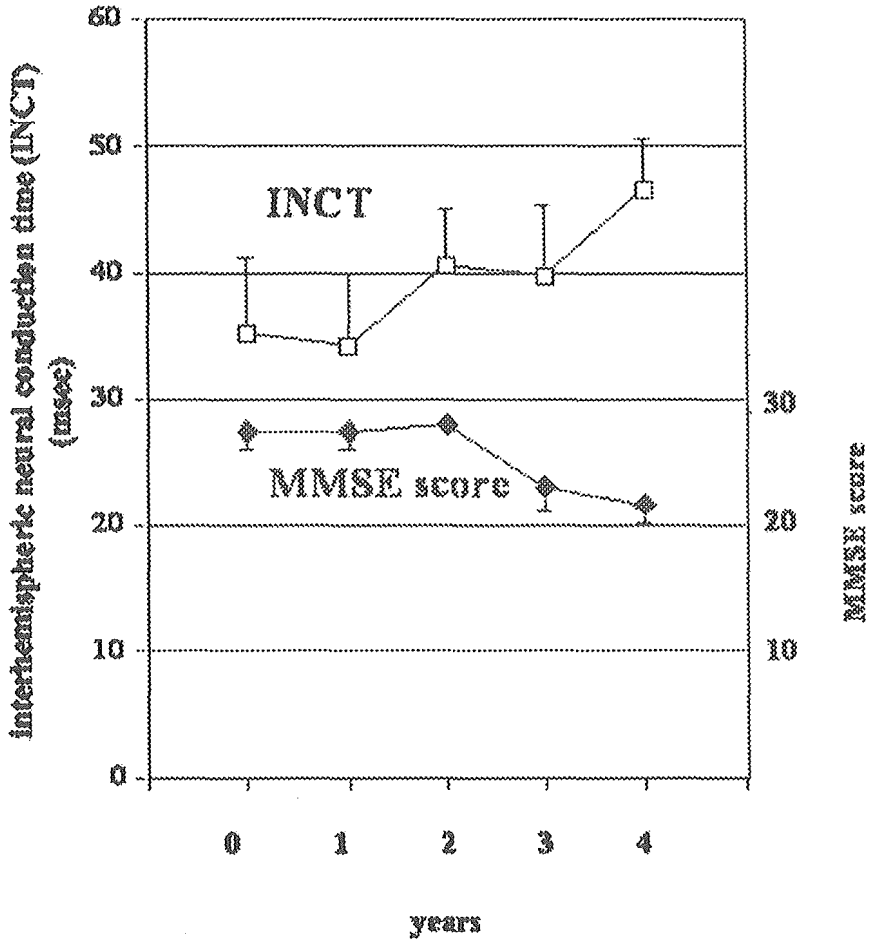


**Figure 3.** Longitudinal changes of INCT and MMSE scores in Group B



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効果的医療技術の確立推進臨床研究事業

分担研究報告書

# めまい感を訴える高齢者の認知機能と脳磁図所見

## 高齢者のめまい感は痴呆の前駆症状か？

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### 緒言

我々は、聴覚誘発磁界計測を用いて慢性めまい感を訴える高齢者の脳機能異常の診断を行ってきた。聴覚誘発磁界計測によって得られた慢性めまい感老人の脳機能異常には二種類があり、その一つは側頭葉神経の異常亢奮、他の一つは左右大脳半球間の神経伝達遅延であった。興味あることに、神経伝達遅延型の群では認知機能低下を示す例の頻度が 31.6%と神経興奮型の 4.8%に比べて有意に高く、また脳磁図所見異常を示さない脳機能正常型の 12.5%と比べても高い値を示した。他に報告したように、大脳半球間神経伝達時間（INCT）は MMSE スコアとの間に有意な負の相関関係を示し、INCT が延長するほど MMSE スコアは低下した。ただし、INCT 延長例であっても MMSE スコアが正常範囲内にある例も多く、INCT 延長が直ちに認知機能の低下を意味するわけではなかった。

我々は、下記に示す代表例に見られるように、慢性フラツキを訴えていた高齢者が当初は認知機能正常であったが長期間経過後に認知機能低下を示すよう

になるという現象を少なからず経験している。そこで、慢性めまい感を訴えて来院し初回脳磁図検査においてMMSEが正常範囲内にあった症例を対象に、その後一年ごとに脳磁図検査（INCT測定）と認知機能（MMSE）検査を反復中である。このような反復計測の結果を後ろ向きに検討し、INCT測定結果が認知機能低下の予測に役立つか否かを検討した。

代表例

YY　71歳男性

主訴：フラツキ

既往歴：狭心症

現病歴：

1990年から狭心症のため国立循環器病センター心臓内科を通院中であった。1993年初め頃から歩行時にフラツキを自覚するようになり、同年11月に脳血管内科に紹介された。

1993年の初診時、血圧は110/62 mmHg、一般理学的所見に異常はなく、神経学的にも明らかな運動麻痺、感覚障害、失調等は認められなかった。歩行は一見正常で、片足立ちは可能、継ぎ足歩行も可能で、本人の「どうもフラフラして仕方がない」という訴えにもかかわらず、外観では起立や歩行に障害はみられなかった。認知機能は正常で、MMSEスコアは26点であった。頭部CTでは脳室拡大と白質病変が認められたが、その程度はほぼ年齢相応と考えられた。

血圧がやや低値を示す傾向があるため心臓内科医になるべく降圧作用の少ない薬剤を投与するよう依頼しながらいわゆる脳循環改善薬等を投与していたが、フラツキが改善しないまま経過した。やがて1997年初めから来院しなくなった。

1999年に長男が頭痛と手のしびれ感を訴えて当科を受診した。その際「お父さんは最近受診されないが、その後、どうなさっていますか？」と尋ねたところ、1997年初め頃から、奇妙な言動、行動を示すようになったので某病院精神科を受診するようになり、その後徐々に病状が悪化して現在では痴呆症として精神病院に入院している、とのことであった。

方法：

聴覚誘発脳磁図では、一側の耳から入力された聴覚信号は同側および反対側の側頭葉に到達して N100m 成分波形を形成する。健常者では同側側頭葉の N100m ピークは反対側側頭葉の N100m ピーク潜時より常に大であり、その潜時差が INCT に相当する。

脳磁図計測に使用した SQUID system は、MC-6400 型、日立磁気計測システムで SQUID センサーは平面型に 8×8 の配列で合計 64 チャネルの平面型磁気計測器である。聴覚刺激は、1kz、90dBnHL の tone-burst 音でのランダム音で、plastic tube を介して一側の外耳口に入力した。反対側の外耳口には masking sound として white noise を入力した。側頭葉に接近させた SQUID センサーで計測された聴覚誘発磁界波形を加算すると、入力された聴覚刺激より約 100msec の潜時を有し最大振幅を呈する N100m 成分が計測される。本研究では右耳より聴覚刺激を行い、左側頭葉および右側頭葉において記録された N100m ピーク潜時差から INCT を計測した。11 例の健常ボランティア（平均年齢 52.3 歳、男性 6 例、女 5 性例、いずれも MMSE スコアは 30 点）で測定した INCT は 15.0 ± 6.1 msec（平均値±標準偏差）であった（表 1）。この健常者 INCT の平均値±2 標準偏差である 27.2 msec 以下を INCT の正常範囲と定義して以下の検討を行った。

対象症例：

対象症例は、慢性的なふらつき感を主訴とする高齢者のうち初回の聴覚誘発脳磁計測の際に MMSE スコアが 24 点以上と認知機能が正常で、その後 4 年間にわたって繰り返し脳磁図検査と認知機能検査を反復施行しえた 11 例である。その年齢、性、初回 *dIrot* 値、MMSE スコア、初回 INCT 値を表 2 に示す。年齢は 58 歳から 84 歳、男性 5 例　、女性 6 例であった。表 2 に示すように、症例 1-7 はいずれも *dIrot* 値が高値を示すが INCT は正常範囲内にある神経興奮型であり（A 群）、症例 8-11 は *dIrot* 値が正常高値を示すが INCT が異常に延長している

伝導遅延型であった（B 群）。これら 11 例はいずれも国立循環器病センター脳血管内科通院中の例ばかりであり、初回測定後ほぼ 1 年間隔で脳磁図検査と MMSE 検査を反復施行した。

結果：

表 2 に 4 年間の追跡可能であった 11 例の年齢、性、初回検査時の *dIrot* 値、MMSE スコア、INCT、SDS スコアを示す。全例の MMSE スコアは 27-30 で、認知機能の低下傾向がみられる例は 1 例もなかった。INCT が正常であった症例 1-7（A 群）は全例が *dIrot* 値が 3.06-5.85 を示すいわゆる神経興奮型であった。うち 7 例中 3 例は SDS スコアが 50 以上でうつ状態を示していた。一方、INCT が異常延長を示した症例 8-11（B 群）は全例が *dIrot* 値が 2.60 以下のいわゆる伝導遅延型であった。これら 4 例ではうつ状態を呈する例はなかった。

表 3-9 にそれぞれ症例 1-7 の追跡検査の結果を示す。症例 1-7 の INCT は 1-4 年後の検査において常に正常範囲内の値を示し続けた。また MMSE スコアも常に 24 以上の正常値を示し続けた。ただし、症例 7 だけは例外であり、3 年後までは MMSE スコアが 26 以上の値を示していたが、4 年後には MMSE スコアが 23 に低下した（表 9）。

表 10-13 にそれぞれ症例 8-11 の追跡検査の結果を示す。症例 8-11 の INCT は初回から異常延長を示していたが、その後も同様の延長またはさらに著明な延長を示し、追跡期間中に INCT が改善傾向を示す例はなかった。症例 8 では 2 年後までは MMSE が正常範囲内の値を示したが、3 年後には MMSE が 22 と異常低値を示すようになり、4 年後には MMSE が 20 とさらに低下した（表 10）。症例 9 においても 2 年後までは MMSE が正常範囲内の値を示したが、3 年後には MMSE が 21 と異常低値を示すようになり、4 年後にも同様の低値が持続した（表 11）。症例 10 では、3 年後までは MMSE が正常範囲内の値を示したが、4 年後になると MMSE が 22 と異常低値を示すようになった（表 12）。症例 11 では、2 年後までは MMSE が正常範囲内の値を示し、3 年後においてもなお正常範囲内の値を示したが、その値は 24 まで低下していた。この例では、4 年後になると

MMSE が 23 と異常低値を示すようになった（表 13）。以上の症例 1-7（A 群）および症例 8-11（B 群）の追跡検査結果のまとめを表 14 に示す。

考察：

以上示したごとく、聴覚誘発脳磁図を用いて計測した INCT は、当初、認知機能が正常なめまい老人 11 例のうち 4 例において異常延長を示していた。これら初回検査において INCT 異常延長がみられた 4 例の MMSE スコアは 26-29 であり、その認知機能はいわゆる mild cognitive impairment の範疇にも入らないほど正常であった。極めて興味あることは、これら 4 例全例が 3 年後または 4 年後に明らかな認知機能障害を呈するようになったことである。過去に我々は 135 例の初回脳梗塞例における認知機能 (MMSE)の追跡調査を行ったことがある。これらの例はいずれも初回脳梗塞発症 1 カ月後の時点で MMSE スコア 24 点以上と認知機能が正常であった例で、その後追跡期間中に脳卒中再発を起こした経歴のみられない例ばかりであった。この追跡調査では初回脳梗塞 2 年後までは、認知機能は正常に維持されていたが、初回脳梗塞 4 年後から約 1/3 の例において認知機能の低下が認められるようになった。今回のめまい感老人の追跡調査においても 2 年後までは認知機能が不変に保たれ、3-4 年後から認知機能低下が始まった点が共通しており、興味深い。初回脳梗塞例の追跡調査の際には、将来生じてくる認知機能の低下を予知できる因子はなかった。しかし、この 11 例のめまい感を訴える老人の場合、聴覚誘発脳磁図で計測した INCT が異常に延長していることが、やがて生じてくる認知機能低下を予知する極めて有力な因子であった。別の報告で述べたように、伝導遅延型を示す群の 32%は認知機能低下を示し、同群における認知機能障害の頻度は神経興奮型や脳機能正常型における頻度より有意に大であった。INCT が MMSE スコアと有意な負の相関を示すことから明らかなように、INCT は認知機能と密接な関連を有するパラメーターである。INCT が異常に延長している例では、たとえ現在の認知機能が正常であっても、3 ないし 4 年後には認知機能低下が臨床的に認められるようになる可能性が高い。

ただし、ここで得られた結論は未だ小数例の結果を基にしたものであり、INCT延長が真に将来の認知機能障害の予測因子であるか否かについては、今後さらなる検討が必要である。

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## 表1　健常者の大脳半球間神経伝達時間
## —右耳刺激時—

| ケース | 右 N100m ピーク潜時 | 左 N100m ピーク潜時 | INCT |
|---|---|---|---|
| 1 | 112　mesc | 100 msec | 12 msec |
| 2 | 96 | 94 | 2 |
| 3 | 100 | 80 | 20 |
| 4 | 108 | 94 | 14 |
| 5 | 96 | 84 | 12 |
| 6 | 100 | 83 | 17 |
| 7 | 98 | 86 | 12 |
| 8 | 124 | 98 | 26 |
| 9 | 98 | 78 | 20 |
| 10 | 104 | 90 | 14 |
| 11 | 104 | 88 | 16 |
| 平均 | 103.6 | 88.6 | 15.0 |
| 標準偏差 | 8.4 | 7.2 | 6.1 |

## 表2　4年間追跡検査を行っためまい感老人11例
## —初回検査時の成績—

| 症例番号 | 年齢/性 | *dIrot* | MMSE スコア | INCT | SDS スコア |
|---|---|---|---|---|---|
| 1 | 84/女 | 5.43 | 30 | 2.0 msec | 57.5 |
| 2 | 59/男 | 5.85 | 27 | 2.4 | 36.3 |
| 3 | 79/女 | 5.17 | 30 | 9.3 | 31.3 |
| 4 | 74/男 | 5.43 | 28 | 10.0 | 50.0 |
| 5 | 74/女 | 3.92 | 30 | 2.9 | 41.3 |
| 6 | 73/女 | 3.06 | 30 | 21.0 | 42.5 |
| 7 | 69/女 | 4.86 | 28 | 12.0 | 50.0 |
| 8 | 68/女 | 2.07 | 26 | 41.7 | 37.0 |
| 9 | 58/男 | 2.33 | 27 | 38.0 | 26.0 |
| 10 | 81/男 | 2.37 | 27 | 32.5 | 32.0 |
| 11 | 73/男 | 2.60 | 29 | 28.0 | 41.3 |