Skin biopsy is useful for the antemortem diagnosis of neuronal intranuclear inclusion disease

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ABSTRACT

Background: Neuronal intranuclear inclusion disease (NIID) is a progressive neurodegenerative disease characterized by eosinophilic hyaline intranuclear inclusions in neuronal and somatic cells. Because of the variety of clinical manifestations, antemortem diagnosis of NIID is difficult.

Methods: Seven skin biopsy samples from patients with familial NIID were evaluated histochemically, and the results were compared with those of skin samples from normal control subjects and from patients with other neurologic diseases. We also examined skin biopsy samples from patients with NIID by electron microscopy.

Results: In NIID skin biopsy samples, intranuclear inclusions were observed in adipocytes, fibroblasts, and sweat gland cells. These inclusions were stained with both anti-ubiquitin and anti-SUMO1 antibodies. Electron microscopy revealed that the features of the intranuclear inclusions in adipocytes, fibroblasts, and sweat gland cells were identical to those of neuronal cells. Approximately 10% of adipocytes showed intranuclear inclusions. No intranuclear inclusions were identified in the skin samples from normal control subjects and patients with other neurologic diseases.

Conclusions: Skin biopsy is an effective and less invasive antemortem diagnostic tool for NIID.

Neurology® 2011;76:1372–1376

GLOSSARY

ALS = amyotrophic lateral sclerosis; **CMT** = Charcot-Marie-Tooth; **DAPI** = 4′,6-diamidino-2-phenyindole di-lactate; **DRPLA** = dentatorubral pallidoluysian atrophy; **FAP** = familial amyloid polyneuropathy; **HD** = Huntington disease; **H&E** = hematoxylin & eosin; **MSA** = multiple system atrophy; **NIID** = neuronal intranuclear inclusion disease; **PD** = Parkinson disease; **PSP** = progressive supranuclear palsy; **SBMA** = spinal and bulbar muscular atrophy; **SCA3** = spinocerebellar ataxia 3.

Neuronal intranuclear inclusion disease (NIID), also known as neuronal intranuclear hyaline inclusion disease, is a progressive neurodegenerative disease characterized by eosinophilic hyaline intranuclear inclusions in neuronal and visceral organ cells.[1-4] Clinical manifestations of NIID are highly variable and can include pyramidal and extrapyramidal symptoms, cerebellar ataxia, dementia, convulsion, neuropathy, and autonomic dysfunction.[1-6] Both sporadic and familial cases have been reported, and the onset of disease varies from infantile stages to late middle age.[1-6] The antemortem diagnosis of NIID is difficult, and most of the reported cases of NIID are diagnosed by postmortem histopathologic examination. Some reports have described antemortem diagnosis of NIID by rectal biopsy[5,6] and sural nerve biopsy.[2] However, rectal biopsy has a risk of perforation,[7] and sural nerve biopsy is applicable only in patients with sensory disturbance.[2] To avoid the difficulty of antemortem diagnosis of NIID by rectal or sural nerve biopsy, we investigated skin biopsy samples from patients with familial NIID and compared the findings with those of samples from normal control subjects and from patients with other neurodegenerative diseases. Our results suggest that skin biopsy is a useful and safe tool for the antemortem diagnosis of NIID.

Editorial, page 1368

e-Pub ahead of print on March 16, 2011, at www.neurology.org.

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Study funding: Supported by a 21st Century Center of Excellence (COE) grant and a global COE grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan and by a grant from the Ministry of Health, Welfare and Labor of Japan.

Disclosure: Author disclosures are provided at the end of the article.

METHODS Subjects. Skin tissue samples were collected from autopsy samples, and skin biopsy samples were collected from patients at Nagoya University Hospital and from normal volunteers. Overall, skin biopsy samples from 7 patients with familial NIID from 2 pedigrees, as we reported previously,[2] were analyzed. Patients with sporadic NIID were not included. For other neurodegenerative diseases, 3 biopsy samples from patients with Charcot-Marie-Tooth (CMT) disease with *PMP22* duplication, 2 autopsy samples and one biopsy sample from patients with familial amyloid polyneuropathy (FAP), one biopsy sample from a patient with genetically diagnosed Huntington disease (HD), 3 biopsy samples from patients with spinocerebellar ataxia 3 (SCA3), 3 biopsy samples from patients with dentatorubral pallidoluysian atrophy (DRPLA), 2 autopsy samples and one biopsy sample from patients with spinal and bulbar muscular atrophy (SBMA), 3 autopsy samples from patients with sporadic amyotrophic lateral sclerosis (ALS), 2 autopsy samples and one biopsy sample from patients with Parkinson disease (PD), one autopsy sample and 2 biopsy samples from patients with multiple system atrophy (MSA), 2 autopsy samples and one biopsy sample from patients with progressive supranuclear palsy (PSP), and 8 samples from normal volunteers were analyzed. All the patients with CMT, FAP, SCA3, DRPLA, and SBMA were assessed genetically.

Standard protocol approvals, registrations, and patient consent. The study was performed with approved protocols and informed consent in accordance with the institutional review board of Nagoya University School of Medicine. Written informed consent was obtained from all patients and normal volunteers.

Skin biopsy, immunohistochemistry, and electron microscopic study. After local anesthesia, a 3-mm-diameter punch biopsy specimen was obtained at 10 cm above the lateral malleolus. All samples were fixed in 10% formalin. Sections of all samples (4 μm) were stained by hematoxylin & eosin (H&E), and immunohistochemical analysis was performed using a Ventana DISCOVERY system (Ventana Medical Systems, Tucson, AZ). Sections were incubated with anti-ubiquitin antibody (Z0458; DAKO, Glostrup, Denmark) and anti-SUMO1 antibody (sc-5308; Santa Cruz Biotechnology, Santa Cruz, CA) using the Ventana DAB Map kit. For immunofluorescence staining, sections were blocked with 4% goat serum and incubated in anti-ubiquitin antibody (P4D1; Santa Cruz Biotechnology). Bound anti-ubiquitin antibody was visualized using antimouse goat immunoglobulin G coupled with Alexa Fluor 488 (Molecular Probes, Eugene, OR). Nuclei were stained with 1.5 μg/mL 4′,6-diamidino-2-phenyindole di-lactate (DAPI). Samples for electron microscopy were fixed in glutaraldehyde in cacodylate buffer and embedded in epoxy resin.[8]

RESULTS We performed more than 30 skin biopsies with no adverse reaction or accident. H&E-stained sections from patients with NIID demonstrated eosinophilic intranuclear inclusions in adipocytes, fibroblasts, and sweat gland cells in the dermis (figure 1, A–C). The nuclei of these cells were strongly stained basophilic, which made it difficult to observe inclusions in such small, dark-stained nuclei (figure 1, A–C). In anti-ubiquitin-stained sections using the DAB technique (figure 1, D–F), intranuclear inclusions were identified easily in all 7 NIID samples. However, erythrocytes and some secreted materials from the sweat glands were strongly stained with the anti-ubiquitin antibody, which made it difficult to distinguish these materials from intranuclear inclusions.

By examination using electron microscopy, intranuclear inclusions in adipocytes, fibroblasts, and sweat gland cells showed common features (figure 1, G–L). These inclusions were composed of filamentous material and showed no limiting membrane. The nuclei of adipocytes were observed as entirely electron dense, but we were able to identify inclusions in the nuclei of adipocytes (figure 1, G and J). The nuclei of fibroblasts were less electron dense than those of adipocytes, and inclusions were recognized easily as electron-dense spherical bodies and filaments arranged in turbinate fashion (figure 1, H and K). In the sweat gland cells, intranuclear inclusions were observed as electron light material in the nucleus (figure 1, I and L).

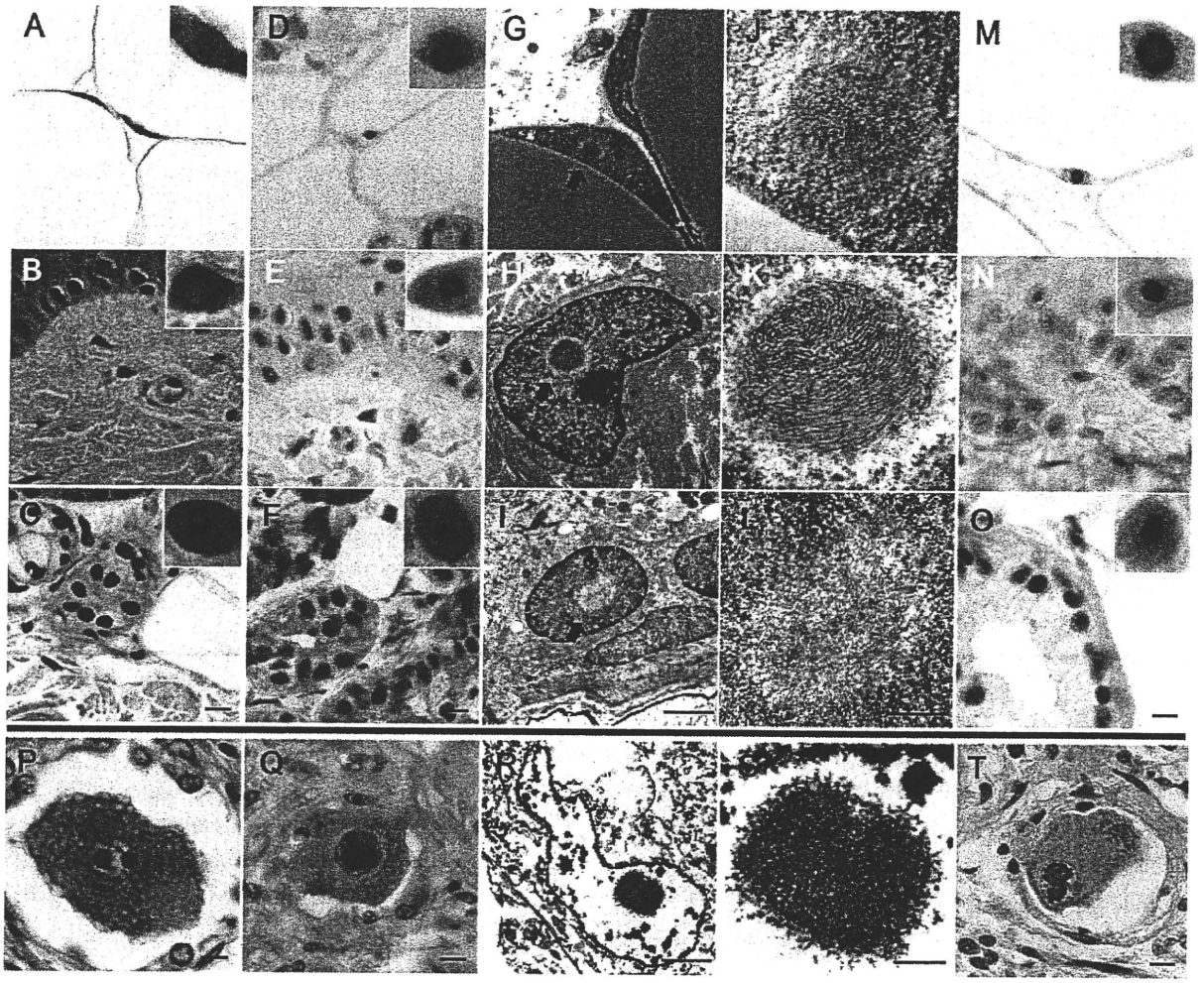
We also examined anti-SUMO1 antibody immunoreactivity. SUMO1 is a small ubiquitin-like modifier protein that covalently conjugates to various intracellular target proteins to alter their cellular distribution, function, and metabolism. Neuronal intranuclear inclusions of patients with NIID are immunoreactive for SUMO1.[9] Intranuclear inclusions in the dermal cells showed anti-SUMO1 immunoreactivity (figure 1, M–O), similar to results previously reported for NIID neuronal cells.[1,9]

These features of inclusions are identical to those of neuronal inclusions in patients with NIID (figure 1, P–T).[2]

Frequency of intranuclear inclusions. We investigated the frequency of intranuclear inclusions in adipocytes, fibroblasts, and sweat gland cells using anti-ubiquitin antibody and DAPI for the purpose of distinguishing intranuclear inclusions from other ubiquitin-positive materials. Intranuclear inclusions were recognized readily as ubiquitin-positive inclusions within DAPI-positive nuclei under merge view (figure 2A). The frequency of intranuclear inclusion–positive adipocytes in NIID skin samples was approximately 10%, which represented the highest frequency among the 3 cell types (table).

Immunofluorescence examination in NIID and a wide range of neurodegenerative diseases. To examine the specificity of skin biopsy for the diagnosis of NIID, we investigated adipocytes in sections of skin samples from patients with NIID and other neurodegenerative diseases that were double-stained with anti-ubiquitin antibody and DAPI (figure 2, A and B). Intranuclear inclusions were not observed in normal control samples (figure 2C). No inclusions were observed in adipocytes from patients with CMT disease and FAP, who show clinical symptoms similar to

Figure 1 Histopathologic features of neuronal intranuclear inclusion disease (NIID) cells



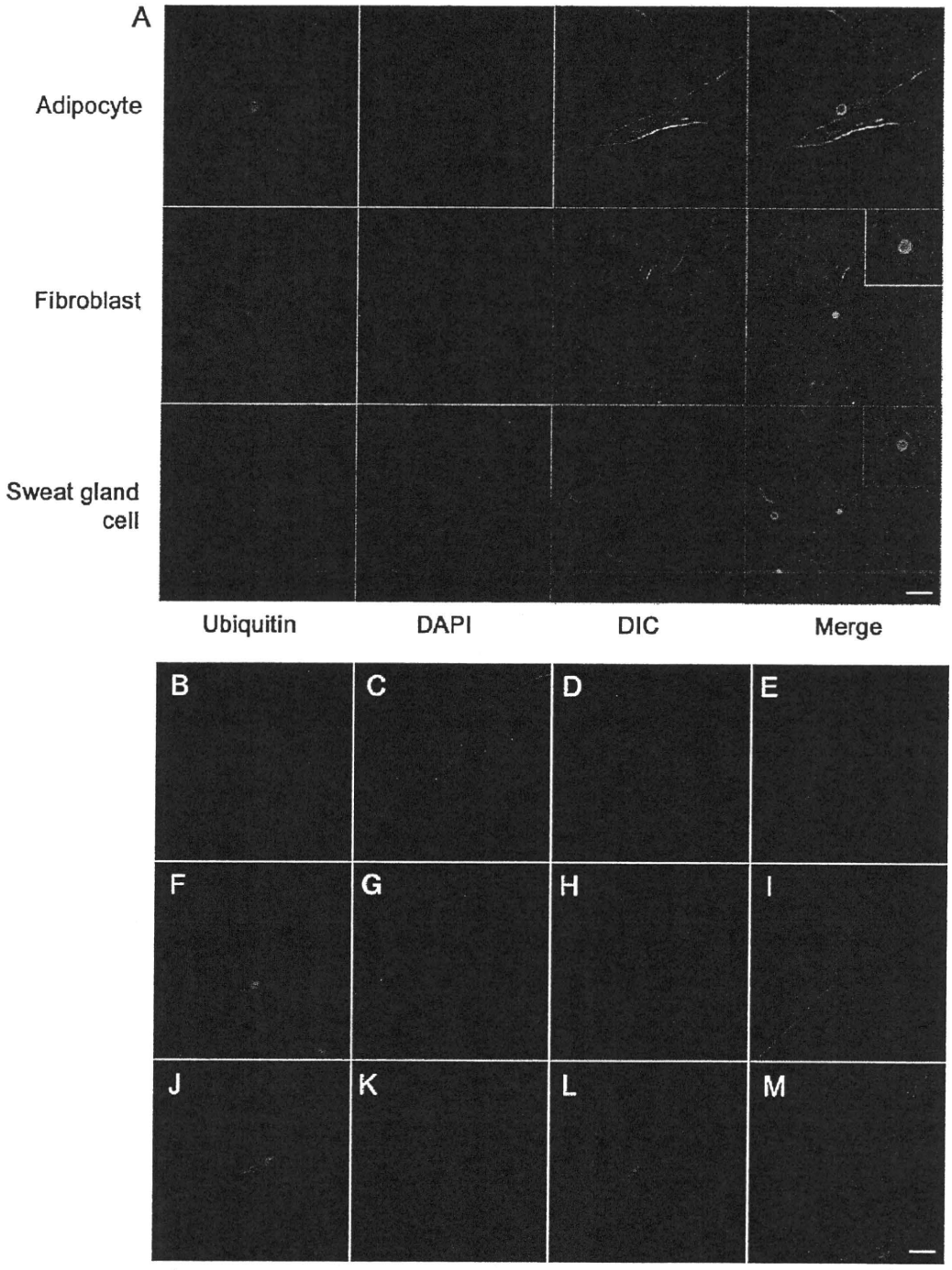
(A–C) Hematoxylin & eosin (H&E) stain of adipocytes (A), fibroblasts (B), and sweat gland cells (C). (D–F) Immunostained samples of adipocytes (D), fibroblasts (E), and sweat gland cells (F) with anti-ubiquitin antibody using the DAB technique. (G–L) Electron microscopic images of adipocytes (G, J), fibroblasts (H, K), and sweat gland cells (I, L). (G–I) Lower magnification view of intranuclear inclusion (arrow). (J–L) Higher magnification view of each intranuclear inclusion. (M–O) Immunostaining with anti-SUMO1 antibody using the DAB technique of adipocytes (M), fibroblasts (N), and sweat gland cells (O). (P–T) Histopathologic features of intranuclear inclusion of neuronal cells of patients with NIID[2]: H&E stain of sympathetic ganglion neuron (P); immunostaining with anti-ubiquitin antibody of dorsal root ganglion neuron (Q); electron microscopic images of astrocyte of anterior horn in lower magnification (R) and higher magnification (S); and immunostaining with anti-SUMO1 antibody of sympathetic ganglion neuron (T). (A–F, M–Q, T) Scale bar = 10 μm. (G–I, R) Scale bar = 2.0 μm. (J–L, S) Scale bar = 500 nm.

those of patients with NIID[2] (figure 2, D and E), or in patients with triplet-repeat diseases (HD, SCA3, DRPLA, and SBMA), ALS, PD, MSA, or PSP (figure 2, F–M). No intranuclear inclusions were observed in fibroblasts and sweat gland cells from normal control subjects and from patients with other neurologic diseases (data not shown).

DISCUSSION In H&E-stained sections from patients with familial NIID, we observed intranuclear inclusions in adipocytes, fibroblasts, and sweat gland cells, but difficulty in observing the inclusions was encountered because of the size and density of the nuclei. Immunohistochemical analysis using anti-ubiquitin antibody with a DAB-based technique revealed intranuclear inclusions more distinctly than H&E staining. These results suggest that double fluorescence staining with anti-ubiquitin antibody and DAPI is a more reliable method to detect intranuclear inclusions in skin samples from patients with NIID, and we recommend this method for the diagnosis of NIID.

Intranuclear inclusions detected in adipocytes, fibroblasts, and sweat gland cells in skin samples were visible in H&E-stained sections, were positive for anti-ubiquitin antibody and anti-SUMO1 antibody, and showed filamentous materials and no limiting membrane. These features of inclusions are identical to those reported for NIID inclusions in neuronal

Figure 2 **Immunofluorescence examination of skin samples from patients with neuronal intranuclear inclusion disease (NIID) and other neurodegenerative diseases**



(A) Double immunofluorescence staining with anti-ubiquitin antibody and 4′,6-diamidino-2-phenyindole di-lactate (DAPI) in NIID skin samples from family I.[2] Intranuclear inclusions were stained with anti-ubiquitin antibody (green) and these inclusions are included in the DAPI-positive nuclei in the merged view. Scale bar = 10 μm. (B–M) Double fluorescence staining for adipocytes in dermis with anti-ubiquitin antibody and DAPI in NIID family II[2] (B), normal control (C), Charcot-Marie-Tooth disease (D), familial amyloid polyneuropathy (E), Huntington disease (F), spinocerebellar ataxia 3 (G), dentatorubral pallidoluysian atrophy (H), spinal and bulbar muscular atrophy (I), amyotrophic lateral sclerosis (J), Parkinson disease (K), multiple system atrophy (L), and progressive supranuclear palsy (M). Scale bars = 10 μm.

Table Frequency of intranuclear inclusions in adipocytes, fibroblasts, and sweat gland cells in patients with NIID[a]

	Adipocytes			Fibroblasts			Sweat gland cells		
Patients	No. of nuclei	No. of inclusions	% Inclusion + nuclei	No. of nuclei	No. of inclusions	% Inclusion + nuclei	No. of nuclei	No. of inclusions	% Inclusion + nuclei
1	204	15	7.4	493	33	6.7	366	13	3.6
2	188	19	10.1	391	18	4.6	195	11	5.6
3	44	7	15.9	215	30	14	111	8	7.2
4	38	5	13.2	456	29	6.4	290	12	4.1
5	59	7	11.9	287	22	7.7	318	14	4.4
6	103	9	8.7	427	37	8.7	91	6	6.6
7	138	12	8.7	397	40	10.1	243	7	2.9
Average ± SD			10.8 ± 3.0			8.3 ± 3.1			4.9 ± 1.6

Abbreviations: DAPI = 4′,6-diamidino-2-phenyindole di-lactate; NIID = neuronal intranuclear inclusion disease.
[a] All patients had familial NIID and were from 2 NIID families that we reported previously.[2] The number of nuclei of each cell type was counted as DAPI-positive nuclei under double immunofluorescence staining. The number of intranuclear inclusions was counted in a merged view of ubiquitin immunofluorescence and DAPI staining (figure 2A).

cells (figure 1).[1-4,9] We suggest that the intranuclear inclusions in dermal cells have a pathologic background similar to that of neuronal cells and are useful for NIID diagnosis. Furthermore, because no intranuclear inclusions were observed in dermal cells from normal control samples and other neurodegenerative disease skin samples, skin biopsy is a powerful tool for the differential diagnosis of NIID from other neurologic diseases.

The examination of a few slides of double-immunostained skin samples may be sufficient for the diagnosis of NIID because the frequency of intranuclear inclusions in adipocytes was approximately 10%. Skin biopsy is an accepted and established technique.[10] It requires only local anesthesia and is safer and easier and presents less stress to patients than rectal biopsy or sural nerve biopsy. Taken together, our results suggest that skin biopsy is an acceptable and less invasive tool for the antemortem diagnosis of NIID.

DISCLOSURE

Dr. Sone reports no disclosures. Dr. Tanaka has received research support from the Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (21659221, 22390175), and a grant from the Ministry of Health, Welfare and Labor of Japan. Dr. Koike has received research support from the Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (21591076), and a grant from the Ministry of Health, Welfare and Labor of Japan. Dr. Inukai reports no disclosures. Dr. Katsuno received research support from the Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (21689024, 2110005). Dr. Yoshida received research support from the Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (21500339), and a grant from the Ministry of Health, Welfare and Labor of Japan. Dr. Watanabe reports no disclosures. Dr. Sobue serves on scientific advisory boards for Kanae Science Foundation for the Promotion of Medical Science, Naito Science Foundation, and has received research support from the Ministry of Education, Culture, Sports, Science and Technology of Japan (21229011, 17025020, 09042025), the Ministry of Welfare, Health and Labor of Japan, and the Japan Science and Technology Agency, Core Research for Evolutional Science and Technology.

Received August 6, 2010. Accepted in final form November 17, 2010.

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(会)

シャルコー―マリー―トゥース病患者診療の現況 全国1次アンケート調査報告*

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Peripheral Nerve 2010; 21(2): 360–361

目　的

シャルコー・マリー・トゥース病（CMT）は進行性の遺伝性ニューロパチーであるが、現在特定疾患に認定されていないため、わが国での診療実態についてのまとまった報告は少ない。その一方で、医療施設で診療されない患者も存在し、患者の実情把握はきわめて重要である。今回、われわれは全国医療機関へアンケート調査を行い、患者の分布・ADL・装具療法など診療実態の把握を試みたので報告する。

対象・方法

医療機関アンケート：全国の神経内科・小児科・リハビリテーション科（リハ科）の教育関連施設と足の外科学会関連施設あわせて計1,841施設に手紙によるアンケート調査を行い、診療されているCMT患者の数・男女比・ADL・装具療法・手術療法・リハビリテーションなどを受けている患者数・外来診療間隔などを記入形式で回答していただいた（2009年10月実施）。

結　果

全国879施設（47.7%）から回答があり、うち244施設で計509名のCMT患者が診療されていた。1施設で診療されている患者数は1人～22人と幅があったが、3人以上診療している施設は73施設であった。性別では、男性284人、女性225人。年齢別では、10歳未満35人、11歳～20歳：74人、21歳～30歳：54人、31歳～40歳：64人、41歳～50歳：67人、51歳～60歳：91人、60歳以上：124人と11歳～20歳に小さいピークがある以外は、高齢者ほど患者数が多かった（図1A）。整形外科関連施設を除くと11歳～20歳に見られたピークは消失した。患者のADLレベルでは、杖なし歩行が58.5%、杖歩行が21.2%、車椅子が19.3%、寝たきりが1%であった（図1B）。医療処置に関しては、短下肢装具使用が31.6%、長下肢装

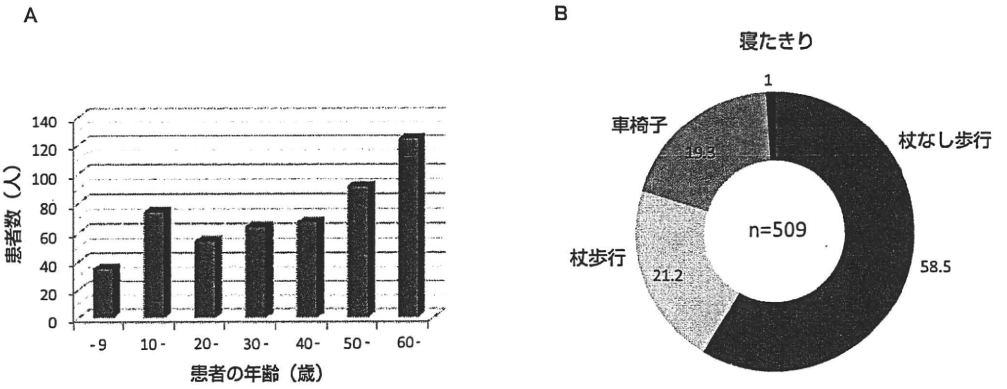

図1　A. 医療機関アンケートによるCMT患者の年齢分布（n = 509）.
B. 医療機関アンケートによるCMT患者のADLレベル（n = 509）. 数は%をしめす.

* A nationwide survey on actual conditions in patients with Charcot Maie-Tooth disease: a preliminary report.

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具使用が1.4%、車椅子使用が12.6%、手術療法を受けている患者が8.3%、リハビリテーションを受けている患者が12.4%、気管切開を受けている患者が1.0%であった。診療間隔は0.5カ月毎～24カ月毎と広く分布していたが、平均値3.69カ月、中央値は3カ月であった。

考　察

CMT患者の年齢分布では、10歳代で小さなピークがある以外は加齢とともに患者数は増えており、CMTは一般的には生命予後がよい疾患であることを示していると同時に、高齢化社会を反映したものと推測される。10歳代に見られる小さなピークは整形外科関連施設を除くと消失し、このピークは成長時期に施行される外科手術のために整形外科で診療された患者数を反映したものと思われた。

患者の約8割の患者は何らかの手段で歩行できている一方で、約2割の患者は車椅子を使用しており、また寝たきりの患者が1%であった。欧米の報告では、脱髄型CMT患者の26%がRankin grade 3以上[1]、あるいは約20%が「重度の身体障害を有する」としており[2]、ほぼ同等の結果と考えられた。CMT自体は生命予後がよい一方で、ADLの低下が本疾患の治療や診療・ケアを考える上で重要と考えられた。

約3割の患者が短下肢装具の装具処置を受けている一方で、長下肢装具をしている患者は1.3%と少数であり、多くの患者は短下肢装具や杖で歩行が確保できない場合、車椅子を使用している実態（12.4%）が浮かび上がってきた。そのなかでリハビリテーションを受けている患者は12.2%と少なくないことが示されたが、その多くはリハ科で診療されている患者であり、リハ科以外に通院されている患者のリハビリテーションの適応判断が今後重要になると思われた。

謝　辞

本研究は厚生労働省研究補助金（難治性疾患克服研究事業）「シャルコー・マリー・トゥース病の診断・治療・ケアに関する研究」（研究代表者　中川正法）の助成によっておこなわれた。

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(会)

右腕神経叢症で発症したneurolymphomatosisの一例*

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Peripheral Nerve 2010; 21(2): 353–354

はじめに

Neurolymphomatosisは悪性リンパ腫の中では比較的稀な病態であるが[1),2)]、腕神経叢症を来すものは約40%と報告されている[2)]。今回われわれは腕神経叢症で発症し、電気生理検査で部位診断し、造影MRIとPET-CTで質的診断をしえたneurolymphomatosisの一例を経験したので報告する。

症　例

症例：82歳女性。76歳時にdiffuse large B cell lymphoma（DLBCL）を発症し、80歳時に再発の既往あり。2009年2月、右母指に異常感覚を自覚、1ヵ月後には遠位側優位の右上肢筋力低下が出現し徐々に増悪、4月に疼痛が出現し増悪したため7月入院となった。

入院時現症：右上肢において手内在筋の筋萎縮、短母指外転筋・小指外転筋・手根屈筋・手根伸筋・上腕二頭筋・腕橈骨筋・菱形筋・前鋸筋の筋力低下を認めた。また、右上肢全体に異常知覚、右手掌に感覚低下を認めた。左上肢および両下肢は運動系・感覚系とも正常であった。右上肢腱反射は消失していた。

検査所見：血算、生化学検査は正常、各種自己抗体も陰性であった。血清、髄液ともに抗s-IL2R抗体も陰性で、髄液細胞診はClass Ⅱであった。

電気生理学的所見：右尺骨・正中・橈骨神経にて、CMAPの低下・Erb-腋窩間での伝導ブロックを認め、右腕神経叢病変が推定された。

画像所見：造影MRIで右腕神経叢に造影効果を認める神経肥厚を認めた。FDG-PETで左鼠径部・左膝窩・右神経叢に沿ってhot spotを認めた。

生検：左鼠径部リンパ節生検・左膝窩皮膚生検で、CD20陽性悪性リンパ腫と診断した。

経過：右腕神経叢でのhot spotも同様の病理であると推測し、右上肢の症状はneurolymphomatosisによる腕神経叢症と考えた。2009年7月中旬に血液内科へ転科し、リツキシマブを併用したDeVIC療法を6コース施行した。同年12月にはFDG-PETでhot spotの消失を認め、右上肢の運動・感覚症状と、Erb・腋窩間の伝導ブロックは改善した。

考　察

腕神経叢症のみで発症したneurolymphomatosisは検索した限りでは9例の報告がある[3)-6)]。うち4例がlymphoma初発例で、5例がlymphoma再発例である。また9例のうち2例で両側の腕神経叢症を認めていた。腕神経叢症はneurolymphmatosisのうちでは約40%と決して少なくなく[2)]、腕神経叢症を診断した際にはneurolymphomatosisを鑑別に考える必要がある。

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* Brachial plexus neurolymphomatosis: A case report.

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