遺伝性ニューロパチー

Charcot-Marie-Tooth病

Charcot-Marie-Tooth disease

中川正法

Key words：遺伝子診断，薬物治療，外科的治療，装具療法，下肢装着型補助ロボット

1. 概念・定義

シャルコー・マリー・トゥース(Charcot-Marie-Tooth: CMT)病は，1886年にCharcot, Marie, Toothの3人によって報告された最も頻度の高い遺伝性ニューロパチーであり，すべての民族に認められる．CMTは一般的に0-20歳頃までに発症し，四肢遠位部優位に障害される緩徐進行性の遺伝子異常による末梢神経疾患の総称である．CMTは正中神経の運動神経伝導速度(MNCV)を基準に，脱髄型(CMT1/CMT4)，軸索型(CMT2)，中間型(intermediate-CMT)に大別される．脱髄型CMTでは，一般的に正中神経のMNCVは38 m/s以下，活動電位はほぼ正常または軽度低下を示し，腓腹神経所見では節性脱髄，onion bulbの形成を認める．軸索型CMTでは，MNCVは正常または軽度低下を示すが活動電位は明らかに低下し，腓腹神経所見では有髄線維の著明な減少を示す．しかし，いずれとも分けられないintermediate-CMTも存在する．CMT関連の原因遺伝子は50種類以上が特定され，我が国においてもCMTの遺伝子診断に関しては大きな進展がみられている．CMTの治療法の開発は不十分であるが，治療法に関する新たな試みが始まっている．

2. 疫　　学

CMTの有病率は，欧米ではこれまで2,500人に1人といわれてきたが，最近の疫学調査でも人口10万人対9.7-82.4人とその頻度は高い[1]．我が国では人口10万人対10.8人との報告があるが[2]，実際の有病率はより高いと推定される．発症年齢は，若年発症(0-20歳)と中年期発症の二相性分布を示す．軽症の高齢CMT患者が見逃されている可能性がある．

3. 病　　因

CMTは，末梢神経の髄鞘，軸索に関連する遺伝子異常によって引き起こされる疾患である．エキソーム解析などのシークエンス技術の進歩によりCMT関連の原因遺伝子は50種類以上が特定されている[http://www.molgen.ua.ac.be/CMTMutations][3-5]．脱髄型CMTの原因遺伝子として，*PMP22*，*GJB1*，*MPZ*など，軸索型CMTの原因遺伝子として，*MFN2*，*GAN1*，*TDP1*，*APTX*，*SETX*などがある．CMTの約半数は*PMP22*重複によるCMT1Aと考えられている(表1)．同一遺伝子の異常であっても，異なる臨床型・重症度を示す遺伝的多様性がある．

4. 臨床症状

CMTは，一般的に四肢，特に下肢遠位部の筋力低下と感覚障害を示す疾患であるが，近年の原因遺伝子の解明に伴い中枢神経系の障害も含む多様な臨床症状が明らかとなってきている．まれに，四肢近位部優位の筋力低下・筋萎縮を示す例や自律神経障害が前面に出るタイプもある．処女歩行の遅れがみられる患者の中には，

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表1　Charcot-Marie-Tooth病(CMT)および関連疾患の病型と遺伝子異常
(文献[3]より改変)

病　型	遺伝子異常	病　型	遺伝子異常
常染色体優性脱髄性CMT(CMT1)		常染色体優性軸索性CMT(CMT2)	
CMT1A	*PMP22*重複	CMT2A1	*KIF1B*点変異
CMT1B	*MPZ*点変異	CMT2A2	*MFN2*点変異
CMT1C	*LITAF*点変異	CMT2B	*RAB7A*点変異
CMT1D	*EGR2*点変異	CMT2B1	*LMNA*点変異
CMT1E	*PMP22*点変異	CMT2B2	*MED25*点変異
CMT1F	*NEFL*点変異	CMT2C	*TRPV4*点変異
HNPP	*PMP22*欠失	CMT2D	*GARS*点変異
		CMT2E	*NEFL*点変異
X染色体連鎖CMT1(CMT1X)		CMT2F	*HSPB1*点変異
CMT1X	*GJB1*点変異	CMT2G	12q12-q13点変異
		CMT2I/J	*MPZ*点変異
常染色体劣性脱髄性CMT(CMT4)		CMT2H/K	*GDAP1*点変異
CMT4A	*GDAP*点変異	CMT2L	*HSPB8*点変異
CMT4B1	*MTMR2*点変異		
CMT4B2	*MTMR13*点変異	常染色体劣性軸索性CMT(ARCMT2)	
CMT4C	*KIAA1985*点変異	ARCMT2A	*LMNA*点変異
CMT4D(HMSNL)	*NDRG1*点変異	ARCMT2B	19q13.1-13.3点変異
CMT4E	*EGR2*点変異	ARCMT2	*GDAP1*点変異
CMT4F	*PRX*点変異		
CMT4H	*FGD4*点変異	常染色体優性中間型CMT(DI-CMT)	
CMT4J	*FIG4*点変異	DI-CMTA	10q24.1-25.1点変異
ARCMT1	*PMP22*点変異	DI-CMTB	*DNM2*点変異
ARCMT1(DSN-CH)	*MPZ*点変異	DI-CMTC	*YARS*点変異

CMT: Charcot-Marie-Tooth, *DNM2*: dynamin 2, *EGR2*: early growth response gene 2, *FGD4*: FGD1-related F-actin binding protein, *FIG4*: phosphatidylinositol 3,5 biphosphate, *GARS*: glycyl-tRNA synthetase, *GDAP1*: ganglioside-induced differentiation-associated protein 1, *GJB1*: gap junction protein, beta 1, *HNPP*: hereditary neuropathy with liability to pressure palsies, *HSPB1*: heat shock 27-kDa protein 1, *KIAA1985*(SH3TC2): SH3 domain and tetratricopeptide repeats 2, *KIF1B*: kinesin family member 1B, *LITAF*: lipopolysaccharide-induced TNF factor, *LMNA*: laminin A, *MED25*: mediator of RNA polymerase II transcription subunit 25, *MPZ*: myelin protein zero, *MFN2*: mitofusin 2, *MTMR2*: myotubularin-related protein 2, *MTMR13*: myotubularin-related protein 13, *NDRG1*: N-myc downstream-regulated element 1, *NEFL*: neurofilament light polypeptide, *PMP22*: peripheral myelin protein 22, *PRX*: periaxin, *RAB7A*: Ras-related protein Rab-7a, *TRPV4*: transient receptor potential cation channel subfamily V member 4, *YARS*: tyrosyl-tRNA synthetase, cytoplasmic.

成長時期に歩行障害の一時的な改善がみられる場合もある．CMT患者のADLは約8割は何らかの方法で歩行が可能であるが，約25％の患者は日常生活で介助を要する[6]．

典型的症状として，凹足(時に扁平足)(図**1**)，ハンマー趾，足関節の変形，歩行・走行困難，たれ足・鶏歩，筋萎縮・筋力低下，下肢優位の感覚障害，腱反射の消失，手指振戦，筋痙攣，疼痛，下肢皮膚温低下(cold feet)，先端チアノーゼを認める．CMT1Aでは，末梢神経の肥厚を認めることが多い．一般的な合併症としては，腰痛，便秘，足関節拘縮，股関節障害などが多くみられる．遺伝子異常のタイプによって，声帯麻痺，自律神経障害(排尿障害，空咳，瞳孔

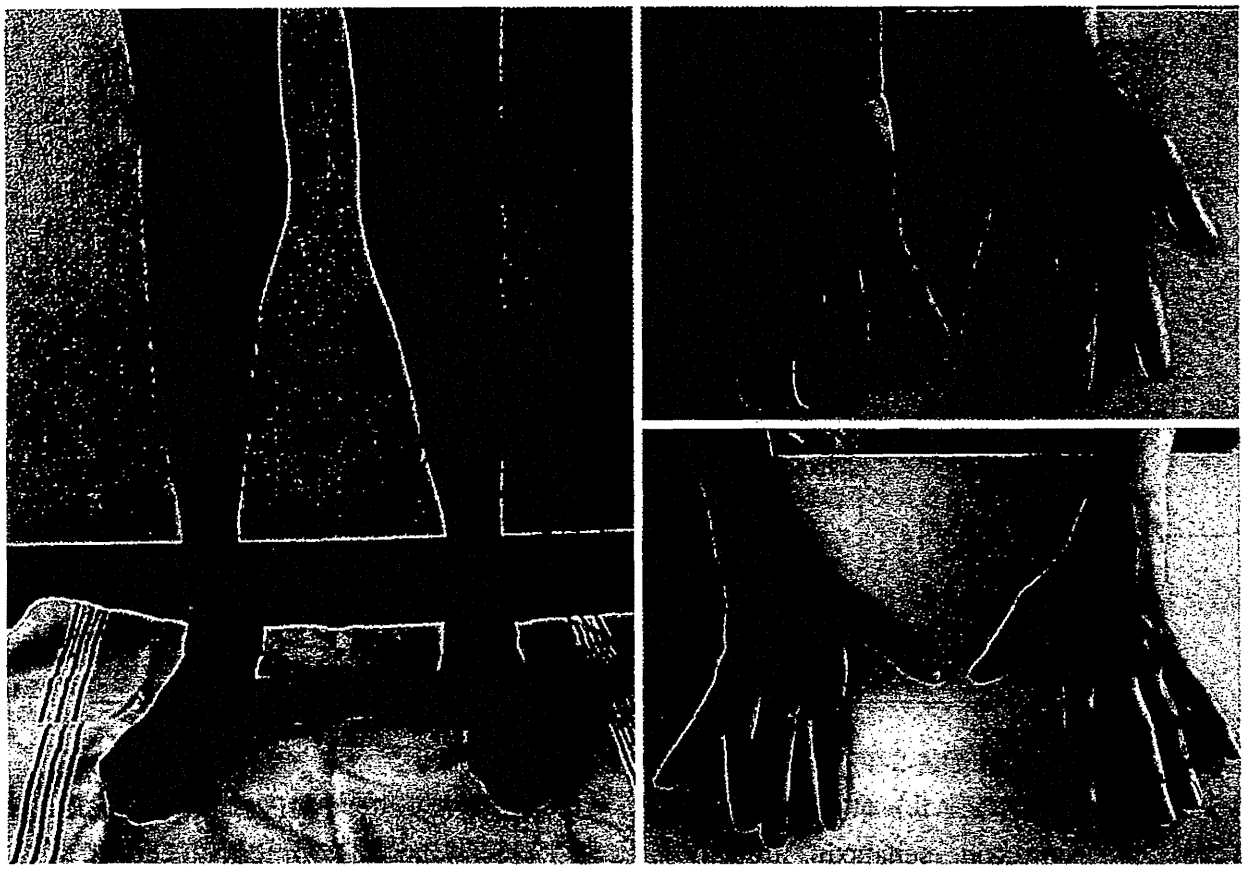

図1 シャルコー・マリー・トゥース病でみられる四肢遠位部の筋萎縮と凹足(文献[6]より引用)

異常), 視力障害, 錐体路障害, 糖尿病, 脂質代謝異常症などの合併がみられる. 重症例では, 呼吸不全をきたし, 人工呼吸器を必要とする場合もある. まれに, 脳神経障害, 声帯麻痺, 緑内障, 視神経乳頭萎縮, 錐体路障害などを示す例もある[7].

CMTの臨床的重症度は, その原因遺伝子の局在にかかわらず, 軸索障害の進行に相関しており, 早期診断, 早期治療が予後に大きく影響する. CMTの早期診断, 早期治療を考える場合, 着床前診断, 発症前診断などの遺伝子診断の倫理的問題は避けられない. CMTに関する遺伝カウンセリングの充実も必要である. 我が国でもCMT患者会が結成され, そのホームページが立ち上げられた[http://www.j-cmt.org/].

5. 診断と鑑別診断

CMTの診断は, 問診, 神経学的診察, 電気生理学的検査, 神経超音波検査, 家系調査, 遺伝子検査[4,5]で行われる. 問診と神経学的診察でCMTが疑われた場合には, 神経伝導検査を行い, 必要に応じて, 針筋電図検査, 神経超音波検査, 腓腹神経生検を行う. 更に, 遺伝子検査にて確定診断となる. *PMP22* のFISH法検査は健康保険が適用される. 正中神経のMNCVを基準に, 脱髄型(CMT1/CMT4), 軸索型(CMT2), 中間型(intermediate-CMT)に大別される. 脱髄型CMTでは, 一般的に正中神経のMNCVは38 m/s以下, 活動電位はほぼ正常または軽度低下を示し, 腓腹神経所見では節性脱髄, onion bulbの形成を認める. 軸索型CMTでは, MNCVは正常または軽度低下を示すが活動電位は明らかに低下し, 腓腹神経所見では有髄線維の著明な減少を示す.

慢性炎症性脱髄性多発ニューロパチー(CIDP), 抗MAG抗体を伴うニューロパチー, 薬剤性ニューロパチー, 虚血性ニューロパチー, POEMS症候群, ビタミンB_1欠乏ニューロパチ

表2　CMT患者の治療に関する最近の報告

対　象	治療薬	内　容
CMT1A	アスコルビン酸	CMT1Aに対するアスコルビン酸のRCTが複数の国で行われた．安全性は確認されたが有効性は認められなかった．
CMT1A	アスコルビン酸	アスコルビン酸のRCT後に12カ月間の追加的オープン試験を5例のCMT1Aに行い，電気生理学的検査では進行がみられたが筋力は有意に改善した．
CMT1A	neurotrophin-3	CMT1A患者8例に150 μg/kg/週3回，24週またはプラセボ投与を行い，NT-3投与群では末梢神経障害スコア(NIS)が改善し，再生軸索が増加した．少数例の検討であり，その後この結果を再現する報告がなく，運動機能の改善はなかったことなどの問題点がある．
CMT1A	PXT3003	Pharnext社がCMT1A 80例を対象にPXT3003(バクロフェン，ナルトレキソン，ソルビトールの合剤)のRCTを2010-12年末にかけて行った．PXT3003は，CMT1Aラットの*PMP22*の発現を抑制し，第2相臨床試験でも安全性と用量依存的に上肢機能が改善した．
CMT1B	クルクミン	*PMP22*点変異(Ser72Leu)を有する15歳女性患者にクルクミンを50 mg/kg/dayを4カ月，その後，75 mg/kg/dayを8カ月，経口投与した．安全性は確認されたが評価指標の改善はなかった．

ー，アルコール性多発ニューロパチー，アミロイドーシス，apratаxin，senataxin，frataxinなど脊髄小脳変性症によるニューロパチー，傍腫瘍症候群，Refsum病，異染性白質ジストロフィー，Krabbe病，Tangier病，遠位型ミオパチー，先天性ミオパチー，筋萎縮性側索硬化症，係留脊髄症候群などとの鑑別が必要となる．

遺伝性ニューロパチーが疑われた場合には，臨床症状，家系調査および電気生理学的検査を行い，遺伝子解析の同意が得られた場合は，新規原因遺伝子同定の最新の情報を踏まえた積極的な原因遺伝子の解明が必要である．

CMTに特異的な血液検査所見はないが，前述の疾患との鑑別に重要である．脱髄型CMTでは，髄液タンパクの上昇や脊髄MRIで神経根の肥厚を認めることがある．

6. 治療と予後

1) 薬物治療

CMTに対する薬物治療として，アスコルビン酸，neurotrophin-3，クルクミン，PXT3003に関する報告がある(表2)．

(1) アスコルビン酸：

CMT1AはPMP22の重複によって引き起こされる病態であり，PMP22はミエリン形成におけるSchwann細胞の分化制御に重要であり，その軸索-髄鞘相互作用に関与している．cAMPはCREBによる*PMP22*プロモーターへの結合を促進し，*PMP22*の発現を増加させるが，アスコルビン酸はこの結合を競合的に阻害することによって，*PMP22*mRNA発現量を低下させる可能性がある．CMT1Aに対するアスコルビン酸の無作為化比較対照試験(randomized controlled trial: RCT)またはオープン臨床試験が国内外で行われたが，いずれの研究でもアスコルビン酸の安全性は認められたが有効性は確認できなかった[8]．

(2) neurotrophin-3(NT-3)：

NT-3を8例のCMT1A患者に150 μg/kg/週3回，24週またはプラセボ投与が行われた．その結果，NT-3投与群では末梢神経障害スコア(NIS)が改善し，再生軸索が増加したとされている[9]．少数例の検討であること，その後この結果を再現する報告がなく，運動機能の改善はなかったことなどの問題点がある．

(3) クルクミン：

クルクミンは秋ウコンやカレー粉に多く含まれている自然の黄色色素である．クルクミンが

表3 CMTに対する外科的治療，リハビリテーション，装具療法に関する研究

対象	内容
CMT 33例	足関節の変形矯正術後の平均56.9カ月後評価では，疼痛，歩行障害が有意に改善し，90％の患者が足変形の矯正に満足していた．
CMT1A 49例	軽症CMTでは利き手の握力とピンチ力が非利き手より強い傾向があるが，重症CMT例では利き手のピンチ力が非利き手よりも有意に低下していた．
CMT1A 10例	ボツリヌストキシンAを6カ月ごとに後脛骨筋と長腓骨筋に注射し24カ月間観察した．凹足の進行予防効果は認めなかった．
CMT 9例	運動療法を20–34カ月間継続したCMT群では対照群と比較して運動機能が維持されていた．
CMT 8例	トレッドミル，ストレッチ，呼吸訓練を週2回，8週間行い足関節角度および6m歩行時間の改善を認めた．
CMT 8例	24週間の運動療法の継続はCMTの副交感神経機能を改善させた．
CMT 26例	普通靴，プラスティック短下肢装具，エラスティックバンド短下肢装具の各装具の効果を比較し，短下肢装具の使用は歩行と姿勢の異常を部分的に改善した．
CMT 30例	4週間連続の足関節の夜間固定と足関節のストレッチングを行い，足関節の夜間固定は背屈角度を改善させた．

変異PMP22タンパクを細胞膜へ解放し，変異*PMP22*発現によるアポトーシスを減少させることが報告されている．動物レベルにおいてもクルクミンは用量依存的に運動機能を改善し，坐骨神経の軸索径を増加させ，Schwann細胞におけるアポトーシスを減少させている．同様の病態が*MPZ*点変異によるCMT1Bの場合にも指摘されており，セサミオイルまたはホスファチジルコリン化クルクミンが*MPZ*R98C変異マウスに有効であると報告された[10]．*PMP22*点変異(Ser72Leu)を有する15歳の白人女性にクルクミンを50mg/kg/dayを4カ月，その後，75mg/kg/dayを8カ月の計12カ月間，経口投与し安全性に問題はなかったが，評価指標の改善はなかったとの報告がある．

(4) PXT3003：

Pharnext社がCMT1A 80例を対象にPXT3003(バクロフェン，ナルトレキソン，ソルビトールの合剤)のRCTを2010–12年末にかけて行った．この3剤の特徴は，既に臨床現場で使用されていることおよび通常用量の1/10～1/100量を使用していることである．2013年6月にフランスSaint–Maloで開催された末梢神経学会でPXT3003の基礎研究と臨床試験の結果が発表された．PXT3003は，CMT1Aラットの*PMP22*の発現を抑制し，第2相臨床試験でも安全性と有効性(用量依存的に上肢機能の改善)が示された[11]．

2) 投与注意が必要な薬物

CMT患者がほかの内科疾患などに罹患した場合，必要に応じて使用される薬剤が末梢神経障害を悪化させる場合がある．特に抗腫瘍薬であるビンクリスチン・シスプラチン・タキソール・サリドマイド・ベルケード，HIV治療薬のジダノシン・ザルシタビン・サニルブジンなどがCMTの症状を悪化させる可能性のある薬剤として有名である[http://www.charcot–marie–tooth.org/med_alert.php]．CMTの臨床症状を示さない潜在的なCMT患者がいる可能性があり，抗腫瘍薬(ビンクリスチンなど)投与前の神経伝導検査の実施は，末梢神経障害の重症化を防ぐ点で可能なかぎり推奨される．

3) 外科的治療，リハビリテーション，装具療法(表3)

関節変形が進行し，装具を用いても足を適切な位置に保てず歩行に支障が出てきた場合．関節の安定性を図るために筋延長術や骨切り術などの整形外科手術が適応となる場合がある．CMTの凹足に対する骨切り術と軟部組織術の短期～中期の手術成績のCMT 33例の後方視的

検討では，疼痛，歩行障害が有意に改善し，90％の患者が足変形の矯正に満足していたとの報告がある[12]．内反尖足の外科治療はCMT患者により安定した歩行をもたらすと考えられるが，その手術適応や外科的治療施行時期についてのより明確な基準作成が必要とされている．CMT患者が手術や出産などのために麻酔を受ける際にも注意が必要である．CMTの重症例では，脳神経障害による嚥下反射の減弱・声帯麻痺・胸鎖乳突筋の筋力低下，自律神経障害による不整脈・低血圧，側彎症による拘束性換気障害，悪性高熱症，術後呼吸不全などの合併に注意すべきである．

'過労による筋力低下(overwork weakness)'についてはこれまでも論議が多い．CMTの症状が軽症である例では利き手の握力とピンチ力が非利き手より強い傾向があるが，重症例では，利き手のピンチ力が非利き手よりも有意に低下していると報告されている．CMTの関節可動域制限の予防のために，発症早期から下腿三頭筋の持続伸張訓練を行う必要がある．日々の生活に運動療法を組み込むことで，疾患の自然経過による進行以上の悪化を抑える効果が期待できる．

装具使用においては，機能障害にあった装具を使用目的と使用時間帯を明確にして，装着することが大切である．短下肢装具の使用，足関節の夜間固定などが有効との報告がある[13]．厚生労働省難治性疾患克服研究事業として，「希少性難治性疾患—神経・筋難病疾患の進行抑制治療効果を得るための新たな医療機器，生体電位などで随意コントロールされた下肢装着型補助ロボット(HAL-HN01)に関する医師主導治験の実施研究」班(研究代表者　中島　孝)が組織され，CMTを含む本格的な臨床治験が開始された．

4) CMTと炎症性ニューロパチー

CMTとCIDPとの合併例の検討から，CMT患者250人に1人がCIDP様の炎症性ニューロパチーを発症すると推定されている．CMT患者で臨床症状の急性悪化を認めた場合には，CIDP様の炎症性ニューロパチーの治療法に準じた対応を考慮してもよいと考える[14]．

5) CMTの経過

CMTの経過は原因となっている遺伝子異常によって異なるが，厚生労働科学研究費補助金難治性疾患克服研究事業CMT研究班[CMT研究班，http://www.cmt-japan.com/index.html]の調査では，短下肢装具使用31.4％，長下肢装具使用1.3％，車椅子使用12.6％，気管切開1.0％，補助呼吸1.1％であった[5]．

CMTに対する有効な薬物療法はいまだ開発されていないが，少しでも良い健康状態を維持することは重要である．手足のケアによる四肢遠位の冷感・浮腫・外傷・胼胝・潰瘍形成の予防，深部静脈血栓症とそれに関連する肺塞栓症の注意なども重要である．CMT患者は消費カロリー/日が健常者より有意に少なく，メタボリックシンドロームが多い傾向がみられる．日常的な運動習慣と食事療法により，'現在の体重を維持する'ことが肝要である[15]．

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Effect of Nicotine on the Pharmacokinetics of Levodopa

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Objectives: Some patients with Parkinson disease improved their symptoms on treatment with nicotine patch or gum. Nicotine has also been studied for its antidyskinetic effect on levodopa-induced dyskinesia. We determined the effects of nicotine on levodopa pharmacokinetics and gastric emptying in healthy subjects and on levodopa transport in Caco-2 monolayers in vitro.

Methods: Healthy subjects received transdermal nicotine patch application followed by oral levodopa/benserazide, 100/25 mg, in a fasting state and with enteral nutrition. Levodopa pharmacokinetics was determined, and gastric emptying was evaluated by carbon 13 (^{13}C)-labeled acetic acid breath testing. In vitro studies using intestinal Caco-2 cell monolayers evaluated whether the intestinal transport of levodopa was affected by nicotine and its metabolite, cotinine.

Result: Nicotine did not increase mean plasma concentration significantly during fasting or with enteral nutrition, although the extent of levodopa absorption was reduced by 34% to 60% in some individuals and the mean plasma concentration of levodopa was statistically decreased by nicotine in subjects who received enteral nutrition. However, gastric parameters were not significantly affected by nicotine. Nicotine and cotinine at 0.1 μmol/L significantly reduced levodopa uptake by Caco-2 cells ($P < 0.01$).

Conclusions: We found that nicotine reduced plasma levodopa concentration in some healthy subjects but with no alteration of gastric emptying rate. In vitro, nicotine inhibited levodopa transport by Caco-2 cell monolayers in an α-methyl amino isobutyric acid-independent, 2-amino-norbornanecarboxylic acid-dependent manner. These results suggest that nicotine may inhibit the transport of levodopa by the system L-amino acid transporter.

Key Words: Parkinson disease, levodopa/carbidopa, nicotine, transporter

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Nicotine has been studied in the symptomatic treatment of Parkinson disease (PD) and with respect to its neuroprotective effect. Various experiments have proven that the protective effect of nicotine is exerted at nicotinic acetylcholine receptors (nAChRs). Functionally, α4β2 and α6β2 subtypes of nAChR play a critical role in regulating striatal activity and behaviors mediated through the dopaminergic system.[1] Treatment with nicotine gum improved the symptoms of juvenile patients with PD.[2] In Parkinsonian mouse models, nicotine improved levodopa-induced dyskinesia (LID).[3]

Absorption of levodopa, the most commonly used and effective treatment of PD, takes place in the small intestine, and factors influencing the uptake of orally administered levodopa are expected to be gastric emptying time, gastric acidity, and active absorption via amino acid transporters in small intestinal cells. Delayed gastric emptying in PD makes longer retaining time for levodopa in the stomach, which triggers its extensive metabolism and further makes less available for absorption.[4–7] Gastric emptying contributes to the variability of plasma levodopa bioavailability, which may affect levodopa delivery to the brain and motor responses in patients with PD. The systemic L-amino acid transporter (LAT) transports large neutral amino acids in Na^+-independent manner.[8,9] L-amino acid transporter transports not only naturally occurring amino acid but also amino acid–related compounds, including levodopa.[10] The uptake of levodopa in human intestinal Caco-2 cells takes place over the apical border via the Na^+-independent, pH-sensitive LAT.[11]

In this report, we determined the effect of nicotine on the pharmacokinetics of levodopa in healthy subjects who were fasting or receiving liquid enteral nutrition, additionally using the $^{13}CO_2$ breath test to determine the effect of nicotine on gastric emptying. In addition, we also determined whether nicotine inhibits the in vitro transport of levodopa in Caco-2 cell monolayers: amino acid transporter inhibitors were applied in this study to confirm that the uptake of levodopa occurred through LAT. Be-cause nicotine has short elimination half-life ($t_{1/2}$) at approximately 30 minutes, we also included its metabolite, cotinine, in this study, as it has a more prolonged $t_{1/2}$ at approximately 20 hours.

MATERIALS AND METHODS

In Vivo Clinical Studies

Oral levodopa/benserazide, 100/25 mg (Chugai Pharmaceutical Co, Ltd, Tokyo, Japan) with or without transdermal nicotine patch application was administered to healthy male volunteers in the morning after an overnight fast using a randomized, crossover design with a 2-week washout period between treatments (Table 1). Levodopa/benserazide was administered with water in study 1 and with enteral liquid nutrition in study 2, with no other liquid or food administration during subsequent experimental procedures. Twelve hours before levodopa administration, transdermal nicotine patch containing 17.5 mg of nicotine (Nicotinell TTS10β, Novartis, Tokyo, Japan) and 35 mg of nicotine (Nicotinell TTS20β, Novartis) were applied in nicotine groups of study 1 and study 2, respectively. All subjects had to refrain from using any nicotine-containing products (with the exception of study medication) for 36 hours before treatment and throughout study assessments. All subjects confirmed written informed consent before study participation. The studies

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TABLE 1. Subjects' Demographics of Study 1 and Study 2

Study 1 in Fasted Subjects (n = 8)	
Age, mean ± SD (range), yrs	30.3 ± 11.1 (23–55)
Height, mean ± SD (range), cm	171.4 ± 6.0 (161–179)
Weight, mean ± SD (range), kg	65.6 ± 8.0 (54–83)
Study 2 in subjects with enteral nutrition (n = 6)	
Age, mean ± SD (range), yrs	25.3 ± 1.5 (23–27)
Height, mean ± SD (range), cm	171.8 ± 5.5 (166–177)
Weight, mean ± SD (range), kg	66.8 ± 3.6 (62–73)

All data are presented as mean ± SD.

were approved by the ethical committee of Ehime Medical University Hospital and were conducted in accordance with the Declaration of Helsinki.

Levodopa Pharmacokinetics

In both clinical studies, blood samples were collected immediately before levodopa administration and every 30 minutes until 240 minutes postdose. Plasma levodopa concentration was measured using high-performance liquid chromatography (HTEC-500; Eicom, Japan) as previously reported.[12]

Assessment of Gastric Emptying Time

The breath samples were exhaled into gas-tight plastic bags at baseline, and every 30 minutes until 120 minutes after taking ^{13}C-labeled sodium acetate dissolved in 200 mL of mineral water in study 1 and dissolved in 200 mL of liquid enteral nutrient (Racol, Otsuka Pharmaceutical Factory, Inc, Tokushima, Japan) in study 2 at the time of levodopa administration. The concentration of $^{13}CO_2$ collected in breath samples was analyzed using an isotope-selective nondispersive infrared spectrophotometer (POCone; Otsuka Pharmaceutical Factory, Inc). The data were analyzed using analysis software for $^{13}CO_2$ breath excretion rate parameters: time when $^{13}CO_2$ of sampled breath air reached the maximum concentration (T_{max}) and the gastric emptying half-life ($t_{1/2}$).

In Vitro Studies

Caco-2 cells were cultured as previously reported.[11] Cell suspensions (0.5 mL) were seeded in collagen-coated monolayer inserts (BioCoat Fribrillar Collagen Cell Culture Inserts, BD Biosciences, Mass). Levodopa (Sigma, St Louis, Mo) at various concentrations (15, 30, 60, 90, and 120 μmol/L) was added to the apical chamber and 1 mL of Hanks balanced salt solution (Invitrogen, Carlsbad, Calif) was added to the basal chamber of monolayers.

We then determined the effect of amino acid transporter inhibitors and low temperature on the cell system. 2-amino-2-norbornanecarboxylic acid (BCH) and α-methyl amino isobutyric acid (MeAIB) are system L- and A-amino acid transporter inhibitors, respectively. 2-amino-2-norbornanecarboxylic acid (Sigma) and MeAIB (Sigma) each at 1 mmol/L were applied in both apical and basal chambers of monolayers with 150-μmol/L levodopa in the apical side of monolayer. To confirm the uptake process takes place in an active transport manner, the monolayer cells were kept at either 37°C or 4°C after adding Hanks balanced salt solution to the basal chamber with 150-μmol/L levodopa solution in the apical chamber.

The effect of (−)nicotine (Wako, Osaka, Japan) and (−) cotinine (Wako) on the cell system was determined.

The concentration of levodopa collected in basal chamber was quantified by high-performance liquid chromatography. The membrane proteins of Caco-2 cell monolayers were quantified by the Bradford protein assay using 10 μg/mL of bovine serum albumin (Bio-Rad, Hercules, Calif) as a protein standard. The amount of permeated levodopa from apical to basal chamber was calculated by the following formula to avoid the bias caused by the amount of proteins in each monolayer: amount of permeated levodopa equals permeated levodopa to basal chamber/amount of protein.

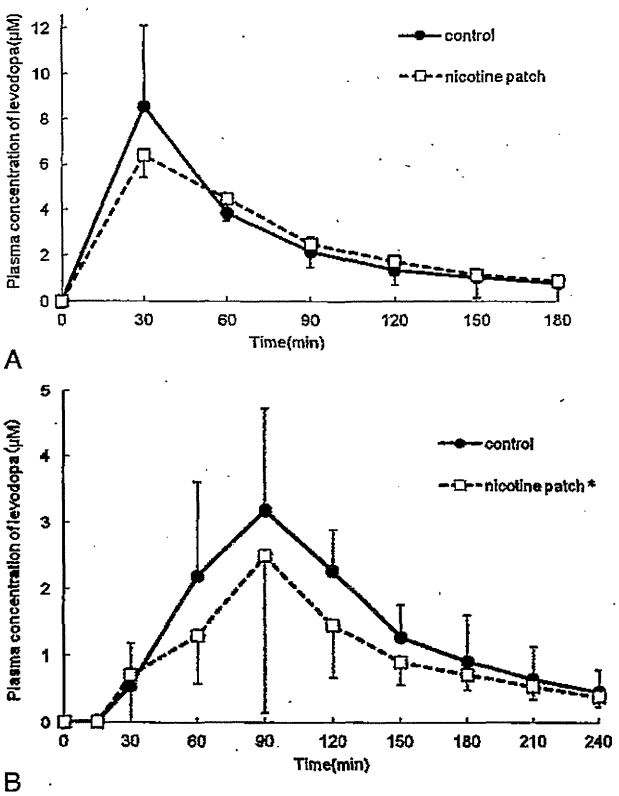

FIGURE 1. Plasma levodopa concentration in fasting healthy subjects (study 1) (A) and those receiving liquid enteral nutrition (study 2) (B) with and without transdermal nicotine patch application. The mean plasma concentration of levodopa was statistically decreased in nicotine patch group comparing with the control group in study 2. All data are presented as mean ± SD. *$P < 0.05$ by 2-way analysis of variance.

TABLE 2. Levodopa Pharmacokinetics Parameters

	Control Group	Nicotine Patch Group
Study 1 in fasted subjects (n = 8)		
C_{max}, mean ± SD (range), μmol/L	8.8 ± 3.1 (4.3–13.2)	6.7 ± 2.5 (3.6–11.0)
$C_{max} - C_{max+30min}$, mean ± SD (range), μmol/L	5.1 ± 2.7 (1.3–9.3)	3.2 ± 2.1 (0.7–6.6)*
T_{max}, mean ± SD (range), min	33.8 ± 10.6 (30–60)	41.3 ± 15.5 (30–60)
AUC_{0-4h}, mean ± SD (range), μmol·min/L	520.0 ± 135.0 (339.2–686.1)	500.0 ± 120.0 (282.6–665.7)
Study 2 in subjects with enteral nutrition (n = 6)		
C_{max}, mean ± SD (range), μmol/L	3.3 ± 1.4 (2.1–5.6)	2.6 ± 2.4 (0.9–6.9)
C_{max}–$C_{max+30min}$, mean ± SD (range), μmol/L	1.3 ± 0.9 (0.4–3.0)	1.4 ± 1.6 (0.3–4.6)
T_{max}, mean ± SD (range), min	95.0 ± 22.6 (60–120)	100.0 ± 52.5 (30–180)
(AUC_{0-4h}) mean ± SD (range), μmol·min/L	333.9 ± 143.8 (210.7–609.6)	243.4 ± 109.6 (136.9–398.3)

All data are presented as mean ± SD. *$P < 0.05$ by paired t-test.

AUC_{0-4h}, area under the plasma concentration-time curve from 0 to 4 hours; T_{max}, time to C_{max}; C_{max}–$C_{max+30min}$, the difference of plasma concentration of levodopa between C_{max} and plasma levodopa concentration at 30 minutes from C_{max} ($C_{max+30min}$).

Statistical Analysis

Paired t test and 2-way analysis of variance were applied to determine the correlation of plasma concentration of levodopa and the gastric emptying time with the application of transdermal nicotine patch. Unpaired t test was used for the uptake study. The level of significance was set to $P < 0.05$.

RESULTS

In Vivo Clinical Studies

Study 1 and study 2 determined the effect of nicotine on levodopa in subjects on fasting and liquid enteral nutrition. Figures 1A, B show the plasma levodopa concentration-time curves in subjects of both studies with a transdermal nicotine patch compared to controls: maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from time 0 to 4 hours (AUC_{0-4h}) for levodopa *did not show significant differences* comparing treatment with and without the nicotine patch (Table 2). The difference of plasma concentration of levodopa between C_{max} and 30 min from C_{max} ($C_{max+30min}$) of nicotine patch group was reduced comparing with control group in study 1. The mean plasma concentration of levodopa was statistically decreased in nicotine patch group comparing with control group in study 2 (Fig. 1B). Six of 8 subjects in study 1 showed a reduction of levodopa C_{max} (by 34% of average)

TABLE 3. Individual C_{max} and AUC of Levodopa in Study 1 and Study 2

Study 1 in Fasted Subjects (n = 8)			
C_{max} (μmol/L)		AUC_{0-4h} (μmol·min/L)	
Control Group	Nicotine Patch Group	Control Group	Nicotine Patch Group
7.49	8.04	510.15	453.30
10.06	5.68	520.50	511.95
5.54	7.86	339.15	471.45
7.86	3.63	409.65	282.60
11.94	10.99	651.00	630.75
13.17	6.48	686.10	546.60
10.20	8.60	663.45	665.70
4.27	3.79	387.15	442.50
Study 2 in subjects with enteral nutrition (n = 6)			
C_{max} (μmol/L)		AUC_{0-4h} (μmol·min/L)	
Control Group	Nicotine Patch Group	Control Group	Nicotine Patch Group
2.56	3.13	267.83	331.13
2.89	6.94	295.43	398.25
4.56	2.23	361.05	283.20
5.63	0.91	609.60	136.95
2.26	1.39	259.05	150.60
2.07	1.35	210.75	160.35

AUC_{0-4h}, area under the plasma concentration-time curve from 0 to 4 hours.

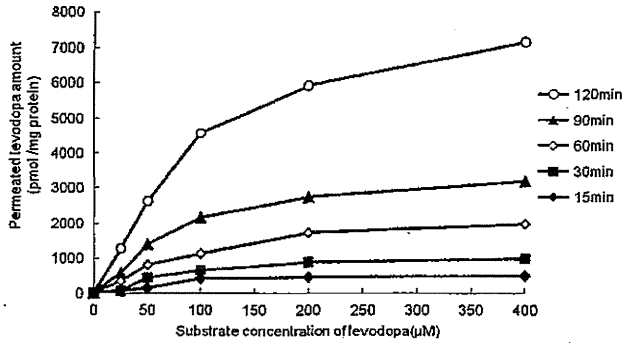

FIGURE 2. Concentration- and time-dependent levodopa uptake in Caco-2 cell monolayers (n = 20).

and 5 subjects showed a reduction in $AUC_{0\text{-}4h}$ (data not shown). Four of 6 subjects in study 2 showed a reduction of levodopa C_{max} (by 60% on average) and also showed a reduction in $AUC_{0\text{-}4hr}$ (data not shown). Subjects in both studies had no adverse effects of drugs.

With respect to gastric emptying parameters, in both studies, there were no significant differences in maximum concentration time (0.6±0.1 vs 0.5±0.4 hour) in study 1 (0.9±0.1 vs 0.87±0.1 hour) in study 2 and $t_{1/2}$ (1.5±0.1 vs 1.4±0.2 hour) in study 1 (1.7±0.3 vs 1.7±0.2) in study 2 comparing the control and nicotine treatments.

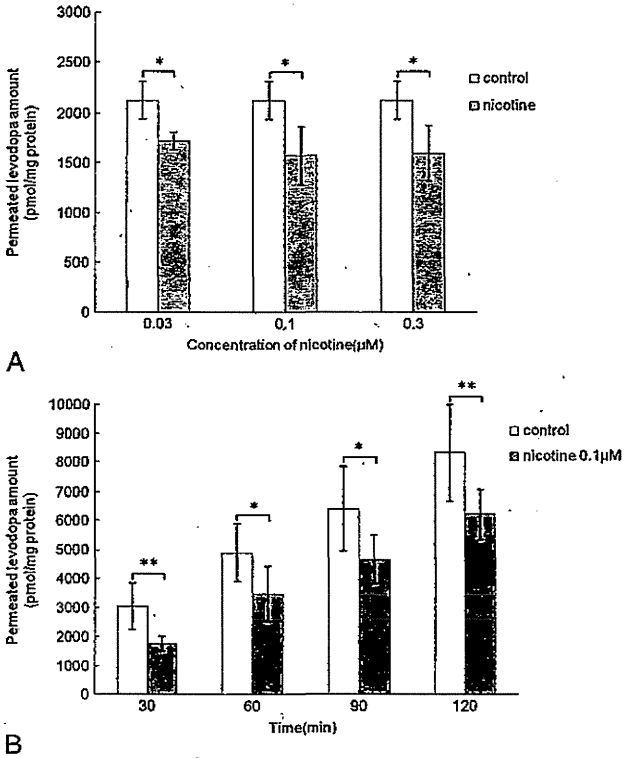

FIGURE 3. Effect of nicotine on levodopa uptake in Caco-2 cell monolayers. A, After 2 hours of incubation with levodopa, 150 μmol/L, in the apical chamber and nicotine (0, 0.03, 0.1, and 0.3 μmol/L) (n = 3, 3, 4, and 4, respectively) in the basal chamber. B, After 0.5, 1, 1.5, and 2 hours of incubation with levodopa, 150 μmol/L, in the apical chamber and nicotine, 0.1 μmol/L, in the basal chamber (n = 8 for both controls and nicotine treatment). All data are presented as mean ± SD. *$P < 0.05$ and **$P < 0.01$ by unpaired t test.

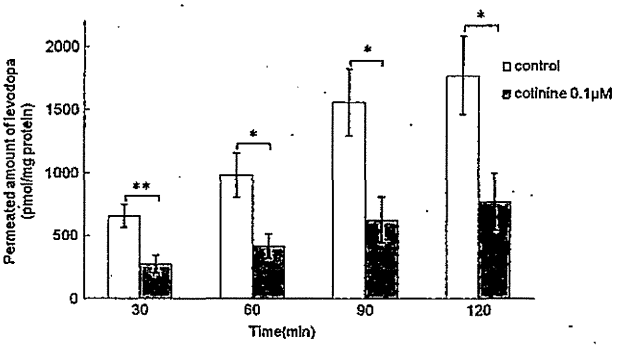

FIGURE 4. Effect of cotinine on uptake of levodopa in Caco-2 cell monolayers. After 0.5, 1, 1.5, and 2 hours of incubation with levodopa, 150 μmol/L, in the apical chamber and cotinine, 0.1 μmol/L, in the basal chamber (n = 3 and 6 for controls and cotinine treatment, respectively). All data are presented as mean ± SD. *$P < 0.05$ and **$P < 0.01$ by unpaired t test.

In Vivo Levodopa Transport Studies

Uptake of levodopa was determined by plotting substrate concentration and intracellular permeated concentration as shown in Figure 2. Saturation of levodopa in Caco-2 cells takes place in a time and concentration-dependent manner. Saturation seemed to plateau at approximately 200 μmol/L. From these data, we set the concentration of levodopa to be 150 μmol/L for the further transport studies of levodopa.

2-Amino-2-norbornanecarboxylic acid, 1 mmol/L (n = 5), decreased the amount of permeated levodopa to a mean of 37.5% compared to controls (n = 4), but MeAIB, 1mM (n = 4), demonstrated no inhibition. The mean permeated amount of levodopa of the control, BCH, and MeAIB were (4175.39 ± 1203.6, 2607.78 ± 928.4, and 4413.47 ± 3452.9) pmol/mg protein, respectively. The amount of permeated levodopa was reduced to a mean of 33.1% when cells were incubated at 4°C compared to 37°C. The mean permeated amount of levodopa incubated at 37°C (n = 6) and at 4°C (n = 4) were (3950.5 ± 381.3) and (2641.1 ± 289.1) pmol/mg protein. These data suggest that uptake of levodopa takes place via BCH-sensitive LAT in a temperature-dependent manner.

Nicotine reduced the amount of permeated levodopa by 24.0% at 0.3 μmol/L (n = 4), 25.3% at 0.1 μmol/L (n = 4), and 18.3% at 0.03 μmol/L (n = 3) compared to controls (n = 3) (Fig. 3A). As the average plasma nicotine concentration of healthy volunteers after applying nicotine patches was approximate 0.1 μmol/L, a concentration of 0.1 μmol/L was deemed suitable for further transport studies. The amount of permeated levodopa was reduced by 25.3% and 54.1% by addition of 0.1 μmol/L nicotine (n = 8) and cotinine (n = 6) in a statistically significant manner (Figs. 3B, 4). Three repeated experiments showed the same results.

DISCUSSION

Parkinsonian rats and monkeys have shown improved parkinsonian behaviors from treatment with nicotine and nicotine agonist.[13,14] Clinically, juvenile patients with PD treated with nicotine gum improved the symptoms.[2] A recent clinical study reported that repetitive finger tapping speed was delayed after taking nicotine with or without levodopa.[15] This study suggested

that at the start of dosing or at low concentration, nicotine induces subthreshold dopaminergic stimulation, which selectively activates the presynaptic D2 autoreceptors, leading to transient motor worsening. Chronic treatment with intravenous nicotine followed by use of nicotine patch improved cognitive performance and motor symptoms in patients with PD; effects last up to 1 month even after nicotine was stopped.[16] A study with high-dose transdermal nicotine showed dramatic improvement in parkinsonism.[17] However, another study of nicotine patches in 32 PD patients showed no improvement.[18]

Levodopa is a gold standard treatment for PD. However within a few years of starting therapy, the duration of benefit of each dose is reduced, which is termed as "wearing-off". The blood concentration of levodopa has been found to be decreased during off periods. It has been demonstrated that gastric emptying is commonly delayed in patients with PD and found to be marked in those with motor fluctuations.[19] A study of gastric emptying in patients with PD showed that it influences and contributes to the variability of plasma levodopa bioavailability.[20] Nicotine patches showed no effect on gastric emptying in healthy volunteers.[21] On the other hand, in a double-blind crossover study of regular smokers who smoked high-dose nicotine cigarettes,[22] the gastric emptying of a solid meal was delayed compared to smoking low-dose nicotine cigarettes. Our study using $^{13}CO_2$ breath test revealed no significant changes in gastric emptying from the application of transdermal nicotine patch. In addition, parameters of gastric emptying were not correlated with plasma levodopa concentrations.

Nicotine is predicted to improve the LID and had been evaluated in studies with rats and monkeys. Nicotine reduced dyskinesia by more than 50% in 6-hydroxydopamine–induced hemiparkinsonian rats, which received levodopa injection.[23,24] In another study with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys,[25] nicotine decreased LID occurrence from levodopa and carbidopa treatment by approximately 50%. A recent study in 6-hydroxydopamine–lesioned mice confirmed that nicotine reduced LID by acting at β2 nAChRs.[3] In our study, some subjects treated with nicotine had reduced levodopa C_{max} and $AUC_{0\text{-}4h}$ when either fasting or receiving liquid enteral nutrition compared to controls. Furthermore, the plasma levodopa concentration curve became smoother under nicotine treatment, which might be the reason for less LID in the patients with PD (Table 2, Fig. 1). Alteration of the plasma pharmacokinetics of levodopa modulates the motor complications in patients with PD.[26] Treatment with nicotine patches might therefore reduce the fluctuation and motor complication in patients with PD, and it does not necessarily mean the neuroprotective effect in patients with PD.

L-amino acid transporter is a Na^+-independent neutral amino acid transporter, which transports naturally occurring amino acids and also amino acid–related compounds including levodopa, whereas system A mediates the sodium-dependent uptake of amino acids with small side chains such as alanine, serine, praline, and glutamine. System A is functionally identified by the transport of *N*-alkylated substrates such as MeAIB. It has been reported that the uptake of levodopa in Caco-2 monolayer cells was sensitive to BCH but not to MeAIB and promoted probably by LAT.[11] In our study, nicotine and cotinine at a concentration of 0.1 μmol/L significantly suppressed the amount of permeated levodopa by 25.3% and 54.1%, respectively. Consequently, we can confirm that the transport of levodopa takes place through LAT as BCH inhibited permeated levodopa, whereas MeAIB showed no inhibitory effect on levodopa transport. Levodopa and plasma large neutral amino acid share the same transporter to cross the blood-brain barrier (BBB).[27,28] Nicotine might also therefore influence the LAT transporter in the blood-brain barrier, which would result in inhibition of levodopa transport to the central nervous system.

Animal model studies have demonstrated that nicotine improved LID by acting at β2 nAChRs. In our study, nicotine reduced the plasma concentration of levodopa in some cases of healthy subjects. Furthermore, we showed that nicotine inhibited the transport of levodopa in the small intestine via LAT. These findings taken together suggest that nicotine has possibility to improve LID in patients with PD. It is known that nicotine may stimulate an endogenous dopaminergic synthesis and may therefore modulate dopaminergic neurotransmission. Therefore, it may act like a MAO-B inhibitor of limited symptomatic effect. This study shows that nicotine-plus-levodopa treatment supports the onset of less fluctuations of levodopa in the periphery.

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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Evaluating the Driving Ability in Patients with Parkinson's Disease Using a Driving Simulator

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Abstract

Objective For patients with Parkinson's disease (PD), driving is challenging due to an impaired motor function and decreased attention capabilities. This study assessed the driving capacity in PD patients by comparing neurological signs.

Methods The driving ability of PD patients was evaluated using a driving simulator (Safety Master NT-932) that tested the reaction time in response to traffic signals and steering wheel errors. We studied the correlations between the total Unified Parkinson's Disease Rating Scale (UPDRS) score, the UPDRS part III score, the subscores of the UPDRS part III score, age, PD disease duration, braking reaction time, steering wheel errors and total scores for driving safety test results. 'On' state regular PD licensed drivers (n=42; mean age: 63 years) in Hoehn and Yahr stages II-III participated after their cognitive status was confirmed using mini-mental state examinations.

Results The UPDRS scores, the UPDRS part III scores and the postural instability subscores exhibited significant ($p<0.05$) correlations with the number of steering wheel errors but not with the braking reaction time or the total safety scores of the test results.

Conclusion The UPDRS is an established evaluation method used to estimate PD signs, although it is not sufficient alone for deciding whether PD patients should be allowed to drive. Our findings suggest that determining the driving ability using a driving simulator might be a useful adjunct to UPDRS scores in the assessment of PD patients who are active drivers. Estimating the driving ability requires complex measurements, including motor performance with perception of stimuli and attention.

Key words: Parkinson's disease, driving simulator, UPDRS

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease that limits movement and sometimes affects the cognitive function. For patients with PD, driving is challenging due to impairment of the motor and non-motor functions. However, there is no universally accepted gold standard for assessing a patient's driving ability. Assessment using a combination of a driving simulator and clinical evaluations can be effective in determining driving safety, although inconsistent findings have been reported in some studies with respect to neurological PD testing and driving performance. A study of 154 PD patients found that driving ability is related to the Hoehn and Yahr scale (1), while no significant correlations were found with an on-road driving test (2).

In the present study, we investigated whether Unified Parkinson's Disease Rating Scale (UPDRS) scores or the PD disease duration can be used to evaluate the driving ability of PD patients by using a driving simulator as the standard for assessing driving ability.

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Figure 1. **Driving simulator (Safety Master-NT 932).**

Materials and Methods

The study was approved by the Ethical Committee of Ehime University Hospital. Written informed consent was obtained from the patients prior to participation in the study, which was performed in accordance with the principles of the Declaration of Helsinki.

PD patients in Hoehn and Yahr stages II or III were recruited for this study. The subjects were regular licensed drivers who participated in the study after they were confirmed to have a normal cognitive status on a mini-mental state examination (MMSE ≥27).

The patients underwent a driving test using a driving simulator (Safety Master NT-932; Niigata Tsushinki Co., Ltd., Niigata, Japan) (Fig. 1) that has been officially adopted at drivers' license centers in Japan. The patients were evaluated for motor ability and perception using simple braking reaction time in response to red traffic signals, braking reaction time in response to variable signals, simple steering wheel technique and complicated steering wheel technique with braking in response to variable signals. The patients were required to handle a steering wheel to avoid colliding with a wall and to respond to changes in the colors of signals on the display by pressing the accelerator or brake pedal as necessary. In the test of simple braking reaction time in response to red traffic signals, the screen of the driving simulator displayed either a black or red traffic light. In the test of braking reaction time in response to variable signals, the patients were required to respond to four traffic lights: red, yellow, blue and black. They were required to press the accelerator in response to black or blue light, release the accelerator in response to yellow light and release the accelerator and press the braking pedal in response to a red traffic light. In the simple steering wheel test, the screen displayed the walls on the left and right sides of the road. The patients were required to avoid colliding with the walls on both sides of the road. In the complicated steering wheel technique with braking in response to variable signals test, the screen of the driving simulator displayed walls on both sides of the road and red, yellow or blue traffic lights on either side of the road. The patients were required to respond to changes in the variable signals by pressing or releasing the pedals while handling the steering wheel to prevent a collision with the walls. The total duration of the test lasted approximately 20 minutes, and the total scores of the safety driving test were rated on a 5-point scale (1 = very poor and unsafe, 2 = moderately poor and unsafe, 3 = marginal, 4 = moderately safe and 5 = a safe driving status).

The PD disease severity was assessed according to the UPDRS score. We evaluated the correlations between the total UPDRS score, the UPDRS part III score, the postural instability and rigidity subscores of the UPDRS part III, the PD disease duration, age, braking reaction time, the number of errors in steering and the total scores of the safety driving test results. Pearson's correlation was applied to evaluate the level of significance, with p values of <0.05 considered to be statistically significant.

Results

A total of 42 PD patients (31 men, 11 women) with a mean (± SD) age of 63±12 years were recruited. As required by the inclusion criteria, all subjects had Hoehn and Yahr staging of II or III with a confirmed cognitive function MMSE score of ≥27.

Both the UPDRS and UPDRS part III scores exhibited a tendency toward a correlation with the simple steering wheel (Fig. 2) and complicated steering wheel with braking in response to variable signals (Fig. 3) errors. The number of errors increased in association with higher UPDRS scores, although there was a significant amount of individual variability in the number of steering errors. The duration of PD was also found to be significantly correlated with the UPDRS and UPDRS part III scores (Fig. 4). However, there were no statistically significant correlations between the UPDRS and UPDRS part III scores and braking reaction time (Figs. 5, 6), the total safety score of the test results (Fig. 7) or patient age (Fig. 8). The postural instability subscore of the UPDRS part III exhibited a significant correlation with errors in the simple steering wheel test (Fig. 9A) and errors in the steering wheel with braking in response to variable signals test (Fig. 9B). However, the rigidity subscores of the UPDRS part III exhibited no correlations with any scores of the driving test (data not shown). The total number of steering wheel errors for the entire cohort exhibited a tendency to increase in association with increasing age and was similar to that observed in the healthy control subjects (Fig. 9).

Discussion

Medical practitioners are required to determine whether or not PD drivers should be allowed to continue to drive a vehicle. A prospective cohort study reported that the baseline factors for discontinuing driving in PD patients are crash history, an advanced age, low driving exposure, impairments in visual perception and cognitive abilities, parkinsonism

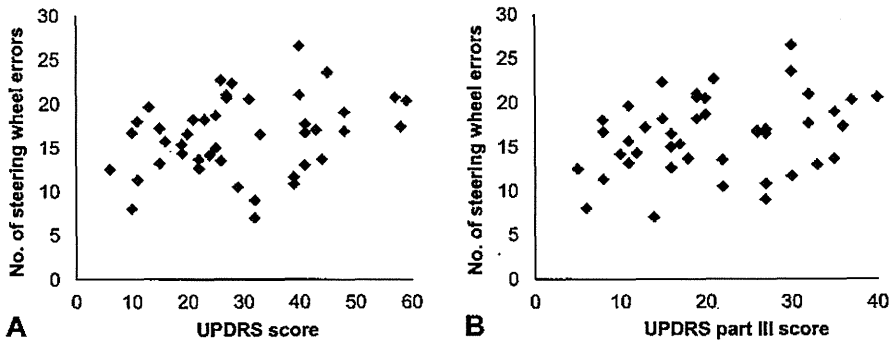

Figure 2. Correlation between the UPDRS scores and the simple steering wheel test. The number of simple steering wheel errors exhibited a tendency to increase ($p<0.05$) in association with increasing UPRDS (A) and UPDRS part III (B) scores.

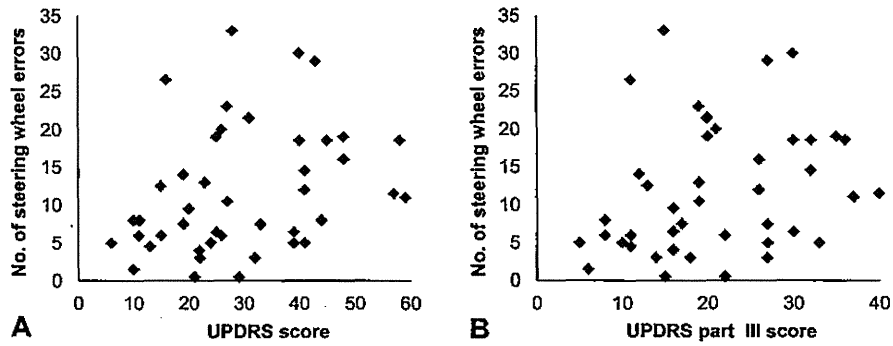

Figure 3. Correlation between the UPDRS scores and the complicated steering wheel under variable signals test. The number of steering wheel errors in response to variable signals exhibited a tendency to increase ($p<0.05$) in association with increasing UPDRS (A) and UPDRS part III (B) scores.

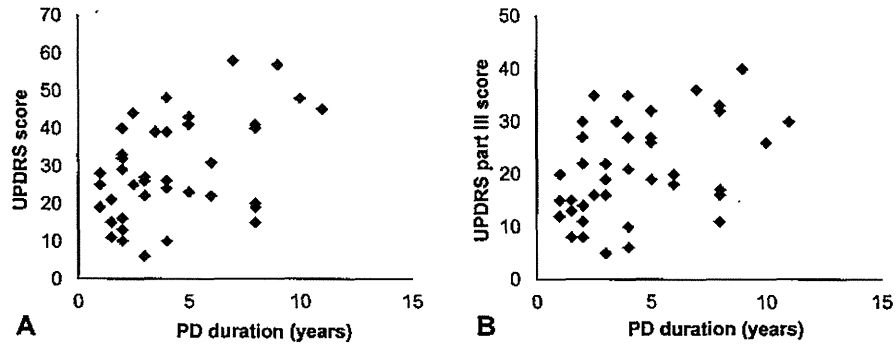

Figure 4. Correlation between the UPDRS scores and the duration of PD disease. The UPDRS (A) and UPDRS part III (B) scores significantly ($p<0.05$) increased in association with longer durations of PD disease.

and higher error counts on road tests (3). More collisions occur in patients with motor impairment and lower MMSE scores (4). PD drivers commit more safety errors on the road compared to age-matched healthy controls (5-7). Studies using driving simulators have also shown that PD patients exhibit delayed deceleration, decreased steering accuracy, slower reaction times and an increased chance of failure to respond to red traffic lights (8, 9). The most common factors for declining safety in PD patients are cognitive decline and visual processing impairment, followed by motor dysfunction and excessive daytime sleepiness (9). The driving performance of PD patients is also predicted by disease duration, visual-spatial processing and the general cognitive and motor functions (10). Audio-verbal distracted driving performance is also worse in PD patients than in controls, with declining visual sensory abilities and cognition and motor functions as causes (11). On-road and simulated driving assessments have been conducted to evaluate the driving

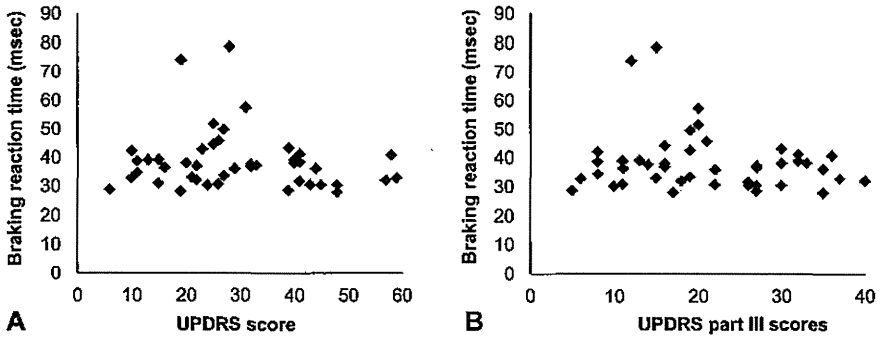

Figure 5. Correlation between the UPDRS scores and the simple braking reaction time. The simple braking reaction time in response to red traffic light signals exhibited no significant correlations with the UPDRS (A) or UPDRS part III (B) scores.

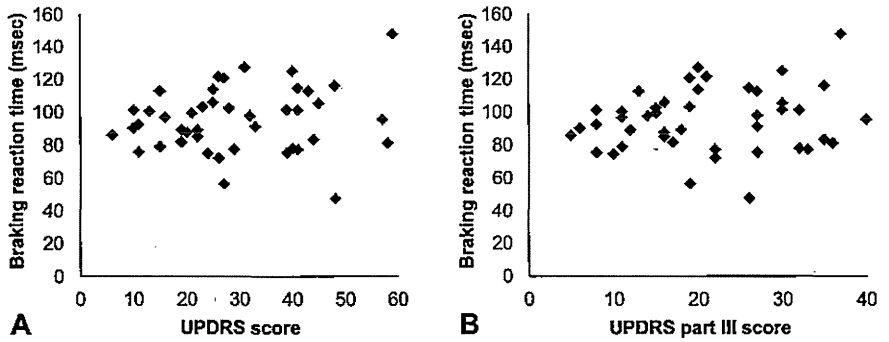

Figure 6. Correlation between the UPDRS scores and the braking reaction time under variable signals. The braking reaction time in response to variable signals exhibited no significant correlations with the UPDRS (A) or UPDRS part III (B) scores.

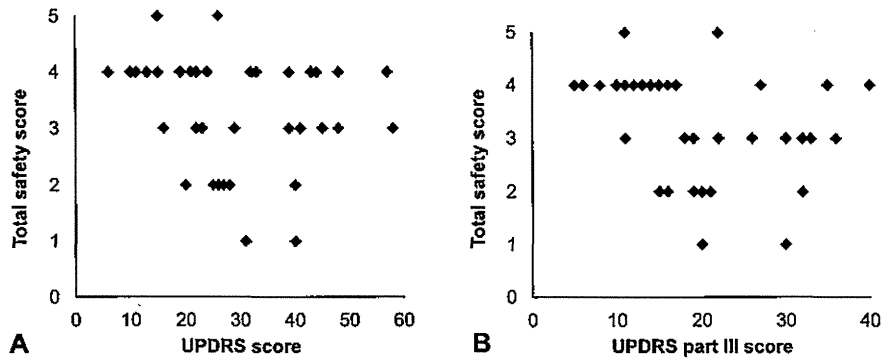

Figure 7. Correlation between the UPDRS scores and the total driving safety test scores. The total driving safety test scores exhibited no significant correlations with the UPDRS scores.

safety of PD patients with mild to moderate disease severity under medication. Webster's rating scale evaluating the 10 key disease criteria of PD, including bradykinesia, rigidity, posture, upper extremity swing, gait, tremor, facies, seborrhea, speech and self-care (12), has also been applied in some studies. In a simulated driving assessment study using Webster's rating scale as the measurement of motor severity in PD patients (8), the Webster's rating scale score was found to be significantly correlated with the driving reaction time, steering accuracy and simple reaction time. However, another study using a similar study design reported that Webster's rating scale is not a predictor of driving assessment in PD patients (13).

In our study, we found that steering accuracy was increasingly impaired in relation to disease severity. Both steering wheel performance and PD disease duration were found to be significantly related to the UPDRS score during the evaluation of driving ability among PD patients using a

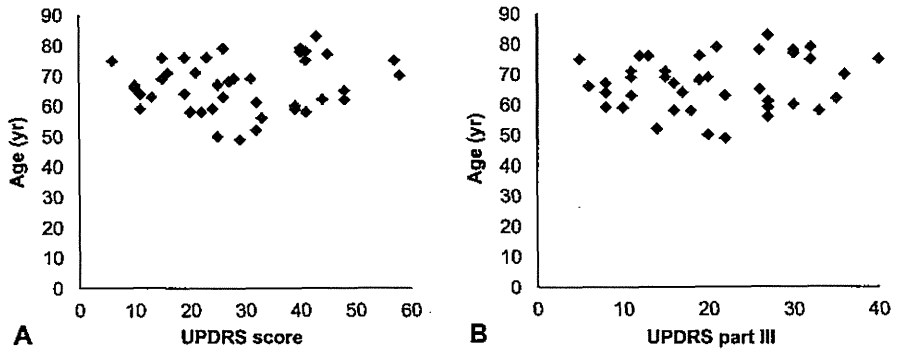

Figure 8. Correlation between the UPDRS scores and patient age. Patient age exhibited no correlations with the UPDRS (A) or UPDRS part III (B) scores.

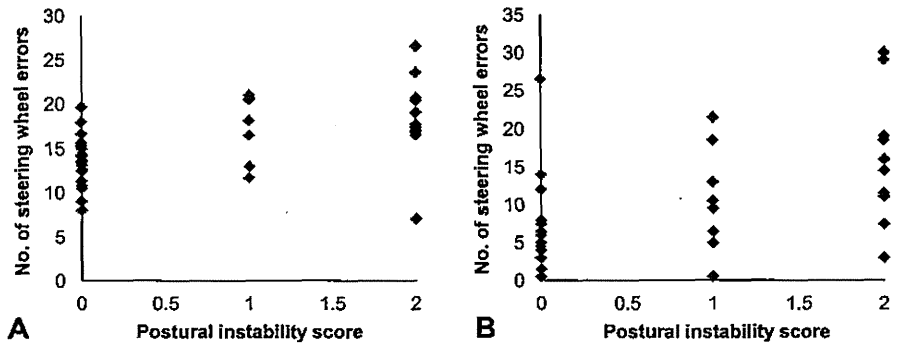

Figure 9. Correlation between the postural stability subscores of the UPDRS part III and the steering wheel test scores. The number of simple steering wheel errors (A) and the steering wheel response to variable signals scores (B) significantly ($p<0.01$ and $p<0.001$, respectively) increased in association with increasing postural instability scores.

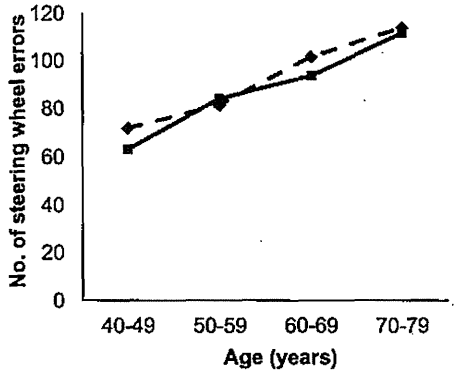

Figure 10. Correlation between the simple steering wheel test and age among the PD patients (solid line) and age-matched control subjects (dashed line). The total number of steering wheel errors in the PD cohort increased in accordance with higher ages. This increase was similar to that observed in the matched control subjects. The values of the normal control subjects were obtained from an in-house document from the driving test simulator manufacturer (Niigata Tsushinki Co., Ltd., Niigata, Japan).

driving simulator. The patients with impaired postural stability made more errors in handling the steering wheel. In contrast, the UPDRS score exhibited no significant correlations with the braking reaction time or the driving safety test results, consistent with the findings of a previous report of on-road assessment (14). The braking action response to traffic signals depends on the perception of stimuli that cannot be assessed by the UPDRS. The UPDRS score alone, therefore, is not adequate to determine whether PD patients should be allowed to drive. Our findings suggest that evaluating the driving ability using a driving simulator might be a useful adjunct to UPDRS scores in the assessment of PD patients who are active drivers.

The authors state that they have no Conflict of Interest (COI).

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Transdermal Rotigotine in Early Stage Parkinson's Disease: A Randomized, Double-blind, Placebo-controlled Trial

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ABSTRACT

Background: We conducted a randomized, double-blind, placebo-controlled trial to determine the safety and efficacy of transdermal rotigotine at doses up to 16 mg/24 hours in patients with early stage Parkinson's disease (PD) in Japan.

Methods: Patients received once-daily rotigotine 2 to 16 mg/24 hours (mean dose, 12.8 mg/24 hours; n = 82) or placebo (n = 90) for 12 weeks. The primary endpoint was the change in Unified Parkinson's Disease Rating Scale (UPDRS) part II (activities of daily living) and part III (motor function) scores from baseline to the end of treatment.

Results: The mean (± standard deviation) changes in UPDRS part II and III scores were −8.4 ± 9.7 in the rotigotine group and −4.1 ± 8.2 in the placebo group and were significantly different ($P = 0.002$). More patients in the rotigotine group than in the placebo group had a ≥20% score reduction. No serious drug-related adverse events were reported.

Conclusions: Rotigotine at doses up to 16 mg/24 hours was well tolerated and improved function in patients with early stage PD. © 2013 International Parkinson and Movement Disorder Society

Key Words: rotigotine; Parkinson's disease; early stage Parkinson's disease; randomized controlled trial

Parkinson's disease (PD) is one of the most prevalent adult-onset neurodegenerative disorders.[1] The most effective treatment for PD is the drug levodopa (L-dopa); however, long-term L-dopa therapy is associated with motor complications, such as wearing-off and dyskinesias, in 20% to 60% of patients with PD.[2–5] Early use of dopamine agonists can delay the onset of motor fluctuations[4–8]; among these, non-ergot derivatives, such as rotigotine, are preferred, because treatment with ergot-derived dopamine agonists can lead to cardiac valvular fibrosis.[9–11]

Rotigotine delivered by a transdermal delivery system (patch) shows agonistic activity toward dopamine D_{1-5} receptors.[12,13] Moreover, the plasma level of rotigotine remains stable for 24 hours after patch application,[14–16] so transdermal patches are associated with more continuous dopamine receptor stimulation, which may prevent dyskinesias.[17] A recent large-scale, double-blind, randomized trial of transdermal rotigotine in patients with PD who had unsatisfactory control of early morning motor symptoms demonstrated that 24-hour treatment was associated with significant benefits versus placebo in terms of the control of early morning motor function and nocturnal sleep disturbances.[18]

Phase 3 trials of rotigotine in patients with early stage PD have been conducted in North America[19,20] and in Europe and other countries[21] with maximum maintenance doses of 6 mg/24 hours and 8 mg/24 hours, respectively. In those trials, rotigotine improved activities of daily living and motor function scores compared with placebo. However, although it was demonstrated that rotigotine at doses of up to 16 mg/24 hours was safe and was as

Additional Supporting Information may be found in the online version of this article.

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