## おわりに

遺伝子解析研究が実を結び，多くの疾患の正確な診断と根本治療へのプロセスを現在，われわれは歩んでいる。高度医療の臨床応用の過程において大切なことは，遺伝子医学というハード面と，その医療を受ける患者，家族への情報提供，支援というソフト面である。クライエント，患者，家族の人権および，生命の尊厳への慎重な配慮が必要である。遺伝子診療が実地医療の一部となりつつある現在，遺伝カウンセリングの重要性は増しており，生命倫理，社会倫理に関する十分な教育と人材育成がなされることも大切である。

## 文　献


1) Resta R et al : A New Definition of Genetic Counseling : National Society of Genetic Counselors' Task Force Report. J Genet Couns 15 : 77-83, 2006
2) UNESCO「ヒト遺伝情報に関する国際宣言(2003)」
http://portal.unesco.org/en/ev.php-URL_ID=17720 & URL_DO=DO_TOPIC & URL_SECTION=201.html
3) 厚生労働省「医療・介護関係事業者における個人情報の適切な取扱いのためのガイドライン（2004)」
http://www.mhlw.go.jp/houdou/2004/12/h1227-6.html
4) 遺伝医学関連学会「遺伝学的検査に関するガイドライン（2003)」
http://jshg.jp/resources/data/10academies.pdf
5) 日本医学会「医療における遺伝学的検査・診断に関するガイドライン（2011)」
http://jams.med.or.jp/guideline/genetics-diagnosis.pdf
6) Bennett RL et al : Recommendations for standarardized human pedigree nomenclature. Am J Hum Genet 56 : 745-752, 1995

総　説

東女医大誌　第81巻　第5号
頁　349～355　平成23年10月

# 小児科領域における研究と治療の進歩

## (11) 遺伝子医療

[1]東京女子医科大学附属遺伝子医療センター
[2]同　大学院医学研究科先端生命医科学系専攻遺伝子医学分野
[3]同　小児科
[4]東京女子医科大学病院輸血・細胞プロセシング部

斎藤加代子(サイトウカヨコ)[1~3]・松尾　真理(マツオマリ)[1,3]・菅野　仁(カンノヒトシ)[1,2,4]・浦野　真理(ウラノマリ)[1]・相楽有規子(サガラユキコ)[1]

(受理　平成23年9月26日)

# Up-to-date Information on Medical Care and Research in Pediatrics
## (11) Genetic Medicine

**Kayoko SAITO[1~3], Mari MATSUO[1,3], Hitoshi KANNO[1,2,4], Mari URANO[1] and Yukiko SAGARA[1]**

[1]Institute of Medical Genetics, Tokyo Women's Medical University
[2]Division of Genomic Medicine, Institute of Advanced Biomedical Engineering and Science, Graduate School of Medicine, Tokyo Women's Medical University
[3]Department of Pediatrics, Tokyo Women's Medical University
[4]Department of Transfusion Medicine and Cell Processing, Tokyo Women's Medical University

Advances in genomic research have made great contributions to the development of genetic medicine. Next-generation sequencing technologies are revolutionizing genomics and genetic medicine by high-throughput analyses of personal genomes. Thus, genetic testing has been used clinically as part of laboratory tests. With more accurate molecular diagnosis, it is possible to predict the prognosis of a patient or make a diagnosis pre-symptomatically or prenatally. In 2003, the UNESCO report on the International Declaration on Human Genetic Data, stated that, "as human genetic data have a special status, appropriate and special protection should be afforded to human genetic data and biological samples." Ethical issues arise in all branches of medicine but particular emphasis is placed on genetics due to the significant impact it has not only on individuals but also on extended families and society in general.

The Institute of Medical Genetics was established in 2004. As genetic testing conveys important genetic information that remains unchanged throughout an individual's lifetime, there are some important issues for discussion. These include protection of an individual's genetic information in computerized medical records system, handling of specimens used in testing, genetic counseling before and after testing, and development of a genetic literacy. Clinical geneticists, physicians and genetic counselors should work as a team to provide the best care for patients and their families.

**Key Words**: genetic testing, ethical issues, genetic counseling, genetic information

### はじめに

ゲノム研究の進歩により，診療の現場において確定診断としての遺伝子検査がなされるようになった．大量のDNA断片の並列シークエンスによる革新的な遺伝子解析技術である次世代シークエンサーの開発により個人ゲノム解析が格段にハイスルー

プット化され，臨床応用される時代となりつつある[1]．従来の臨床検査，さらに遺伝子検査でも診断が困難であった症例で確定診断がつく可能性も高くなってきている．そのような背景において，発症リスクを有する人々における発症前診断，保因者診断，さらに出生前診断も可能な時代となった．遺伝子情報は個人と血縁者で共通性があり診断結果が血縁者に影響を及ぼす場合がある．遺伝子情報漏洩の危険性，遺伝的差別への危惧など倫理的法的社会的問題が生じる可能性もある．診療においては，遺伝カウンセリング実施体制の構築と遺伝子情報の管理が重要である．また，わが国の医療事情や倫理的問題に対処でき，オーダーメイド医療にも対応できる人材の育成が求められている．2004年に創設された本学遺伝子医療センターにおける遺伝子医療と東京女子医科大学病院の電子カルテにおける遺伝子情報管理について解説する．

**1．遺伝性疾患と遺伝子検査―単一遺伝子病と多因子遺伝病―**

1）単一遺伝子病

一種類の遺伝子変異を原因とする疾患を単一遺伝子病という．染色体上の遺伝子変異により発症するメンデル遺伝病と，ミトコンドリアにおける遺伝子変異により発症する疾患が含まれる．単一遺伝子変異のすべてが疾患になるわけではないが，何らかの遺伝形質発現の原因になり得る．生まれてくる子どもの1～2%に何らかの先天性の異常を認めることが分かっており，現在，2万を超える遺伝形質が知られている．メンデル遺伝病は，常染色体優性遺伝，常染色体劣性遺伝，X連鎖優性，X連鎖劣性の遺伝形式をとる．

遺伝子検査は単一遺伝子病における確定診断の方法として発展してきている．例えば家族性腫瘍であれば，DNA配列における変異が明らかになることにより，腫瘍の早期発見・治療がなされ，家族における遺伝に関する問題を明らかにすることが可能となる．腫瘍摘出による早期治療に結びつくこともある一方で，患者・家族にとって，自身や子どもにも同様の疾患が出るのか，他の親族への影響はどうか，など具体的な検査動機となる．確定診断につながる遺伝子検査であれば有効な治療法が確立されていなくても，自然歴情報を入手することで医療管理方針決定が可能となり，その他の無駄な検査を回避できるなどメリットがあるため，被検者が未成年であっても検査の適応となる場合が多い．一方で，発症前診断，保因者診断の場合には，症状がない個人が検査の対象となるため被検者の「知る権利」と「知らない権利」を守るために，発症時に有効な治療法が確立されている疾患の場合を除いては，未成年者の検査は回避されるべきである．さらに成人であっても，本人の自発的意思に基づいているか，時期や状況が妥当か，フォローアップ体制が整っているかなど，万全の体制で臨む必要がある．着床前診断を含む出生前診断の場合には，検査を希望し同意する親と被検者である胎児の立場が異なるため，検査の実施にあたっては疾患ごとの議論と症例ごとの慎重な対応が必要不可欠である．

2）多因子遺伝病

複数の遺伝子変異と環境要因が相互に影響して惹起される疾患を多因子遺伝病という．先天奇形，糖尿病，高血圧，高脂血症，肥満，癌などが含まれる．浸透率あるいは個々の遺伝子の表現型に及ぼす効果がそれほど高くないという特徴がある．罹患者の頻度が高く，かつ環境因子の調整による発症予防，早期発見，早期治療が可能となることから，ゲノムワイドな研究が進み，予測的遺伝学的検査としての易罹患性検査の開発が求められている．ただし，これら多因子遺伝病の発症予測に用いられる遺伝学的検査，特に体質遺伝子検査においては，検査の分析的妥当性，臨床的妥当性，臨床的有用性，環境因子の分析を含むコホート研究と確率的解析による科学的根拠を明確にする必要がある．「肥満遺伝子検査」や「子どもの能力判定遺伝子検査」など，頬粘膜でDNAを採取できる手軽さから，分析的妥当性に欠ける遺伝子検査を実施する健診クリニックや検体を直接に検査会社に送って分析結果を得るようなDirect-to-Consumer(DTC)遺伝子検査を実施する検査企業が現れてきている[2]．体質遺伝子検査と呼ばれている遺伝学的検査の多くは，個人の体質を確実に表すもの，あるいはある疾患を発症するかどうかについて明確な答えを与えるものではなく，体質あるいは発症のリスクについて，その確率を示しているにすぎない．またその検査の有用性が科学的に証明されているものは極めて少ないのが現状である[3]．将来的には適切な運用により個別化健康増進が可能となると考えられるが，一方で営利目的の検査のみが先行してしまう場合や，妥当性・有用性が不明瞭な場合など問題点が少なくない．

**2．遺伝性疾患に対する対応**

「遺伝医学関連学会による遺伝学的検査に関する

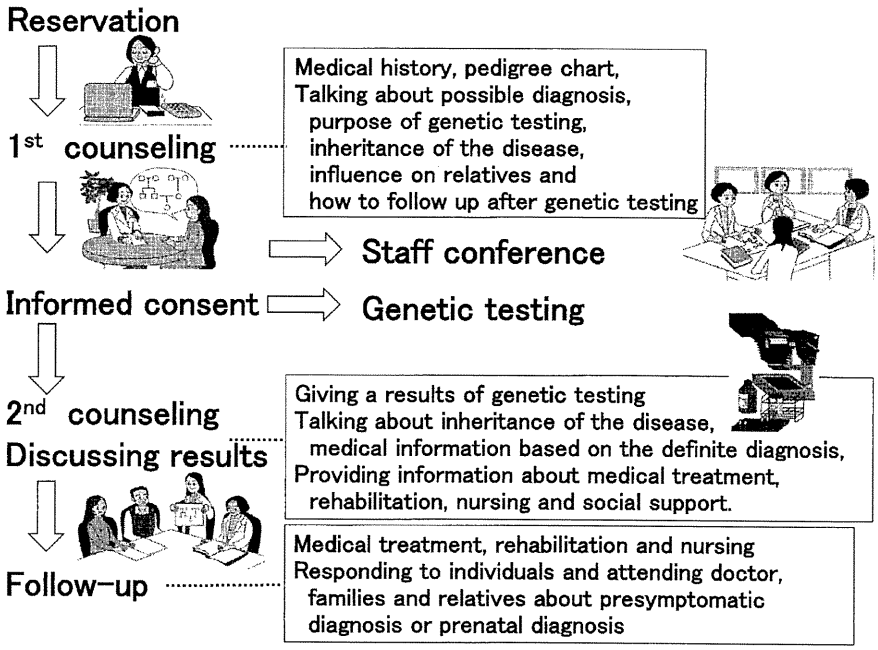


**Fig. 1** Genetic outpatient clinic practice at the Institute of Medical Genetics, TWMU

ガイドライン(2003)」[4]は，遺伝学的検査が医療全域にわたって広く有効に利用される時代に対応して，2011年に日本医学会「医療における遺伝学的検査・診断に関するガイドライン」[5]として改訂がなされた．この改訂では，すでに発症している患者の診断目的として行われる遺伝学的検査において，各診療科の医師自身が遺伝に関する十分な理解と知識および経験をもつことが重要であり，検査の意義や目的の説明と共に，結果が得られた後の状況や検査結果が血縁者に影響を与える可能性があることなどについて十分に説明し，被検者が理解して自己決定できるように支援する体制を整えることを述べている．医療機関は，遺伝医学の基本的事項および個人の遺伝情報の取扱いに関する啓発や教育を行い，適切な遺伝医療を実施できる体制を整備することが望まれる．

1）単一遺伝子病に対しての対応

Fig. 1に示すように，遺伝子医療センターにおける診療は，遺伝カウンセリングと遺伝子検査を中心としている．初回の遺伝子診療において，患者とその家族の疾患に関する状況（主治医からの紹介状，発端者本人の症状，経過，検査所見など），家族歴を聴取し，家系図を描く．家系図は遺伝子診療の基本である．Fig. 2に家系図を記録する場合に用いる記号の主なものと家系図の一例としてX連鎖劣性遺伝形式をとる副腎白質ジストロフィーの家系を図示した[6]．できるだけ詳しく，3世代位は遡って情報を得ることが望ましい．家系図を分析することにより単一遺伝子病における遺伝形式がわかり，疾患の診断がなされたり，否定されたりする．例えば，各世代の男女に同様の疾患の患者が認められるとき，常染色体性劣性遺伝は考えがたい．また，母親を介して疾患が遺伝していることが考えられるとき，X連鎖性疾患やミトコンドリア病を考える．父と息子が同様の疾患であるとき，X連鎖性の疾患は否定される．

遺伝カウンセリングを実施するには，疾患の臨床診断がなされていることが重要であり，筋ジストロフィーにおいても，脊髄性筋萎縮症においても，臨床診断が違うと遺伝形式が異なり，また遺伝子検査を実施しても，原因の遺伝子変異の同定ができない．そして，誤った情報に基づく遺伝カウンセリングとなる．

2）薬理遺伝学（pharmacogenomics：PGx）検査における対応

薬剤の効果や副作用の予測としてのPGx検査に関わる遺伝子診療[7]は，これからの重要なゲノム医療のフィールドである．薬に対する反応などの体質の違いを遺伝子多型から予測し，遺伝子の情報をもとに個人個人にあった治療をすることである．薬の効果が高いかどうか，副作用を起こしやすいかどうかを予め遺伝子多型で調べる．効果が高い薬剤や，副作用がでない薬剤を選択することにより，安全で有効な治療が期待できる．例えば，てんかんに対して抗けいれん剤を用いたり[8]，がんに抗がん剤を使う場合[9]

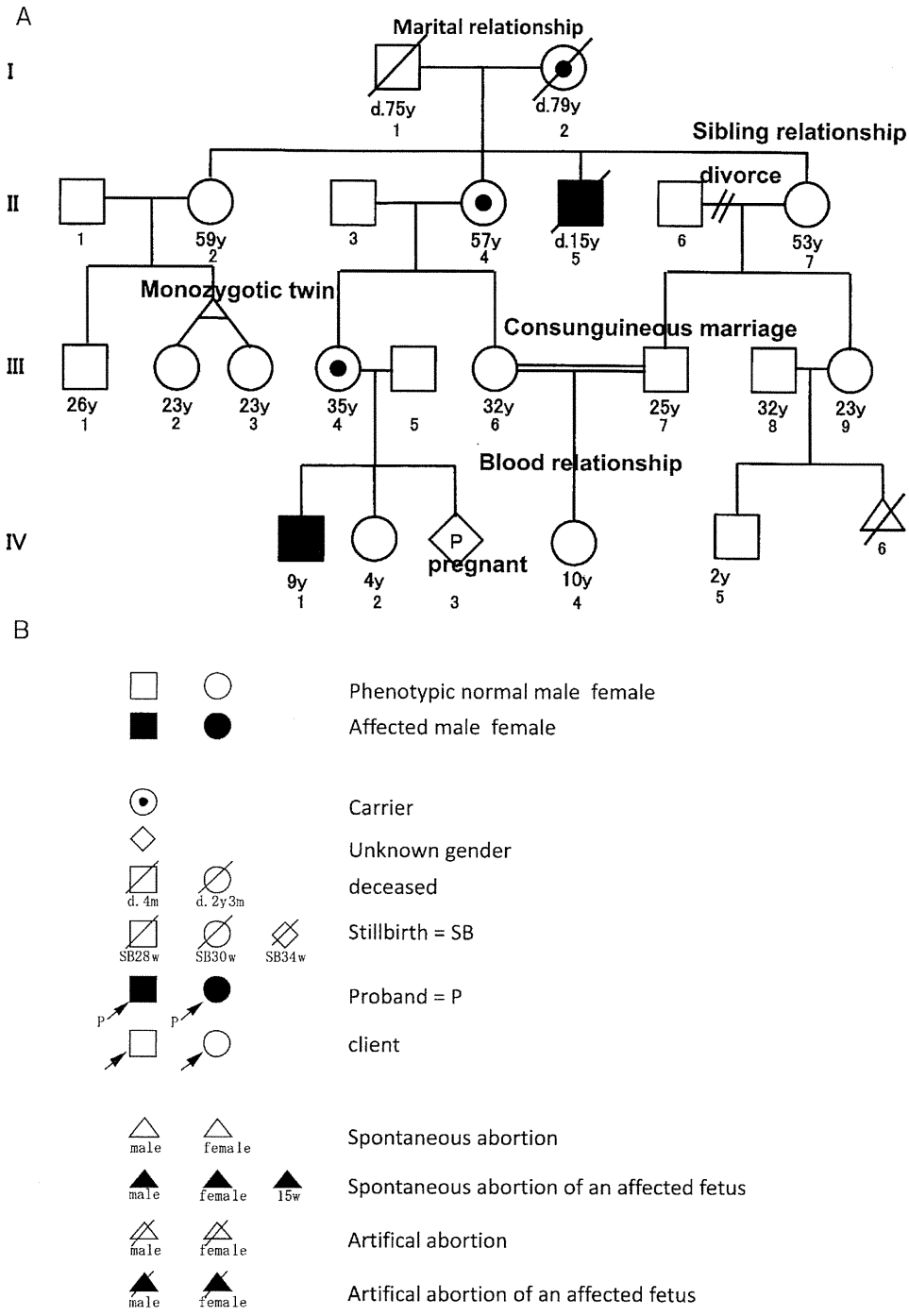


**Fig. 2**

A: Standardized pedigree chart nomenclature: A family with adrenoleukodystrophy.
B: Symbols of the pedigree chart.

においても，遺伝子情報をもとに，抗けいれん剤や抗がん剤について，個人個人への効果や副作用の起こしやすさを事前に予測し，薬剤を適正に使用することができれば，副作用を避けられる可能性がある．

薬物の動態に関連する遺伝子は Fig. 3 に示すようにひとつの薬でも吸収，分布，代謝，排泄のプロセスにおいて，複数のトランスポーター，受容体，イオンチャネル，代謝酵素などが関わっている．従って，ある遺伝子多型であれば「必ず副作用が出る」とか「必ず効果が強い」，などと確定的なことはいいがたい．現在のところ，薬理遺伝学は 100% の予測ではない．しかし，診療に応用するメリットは高い．

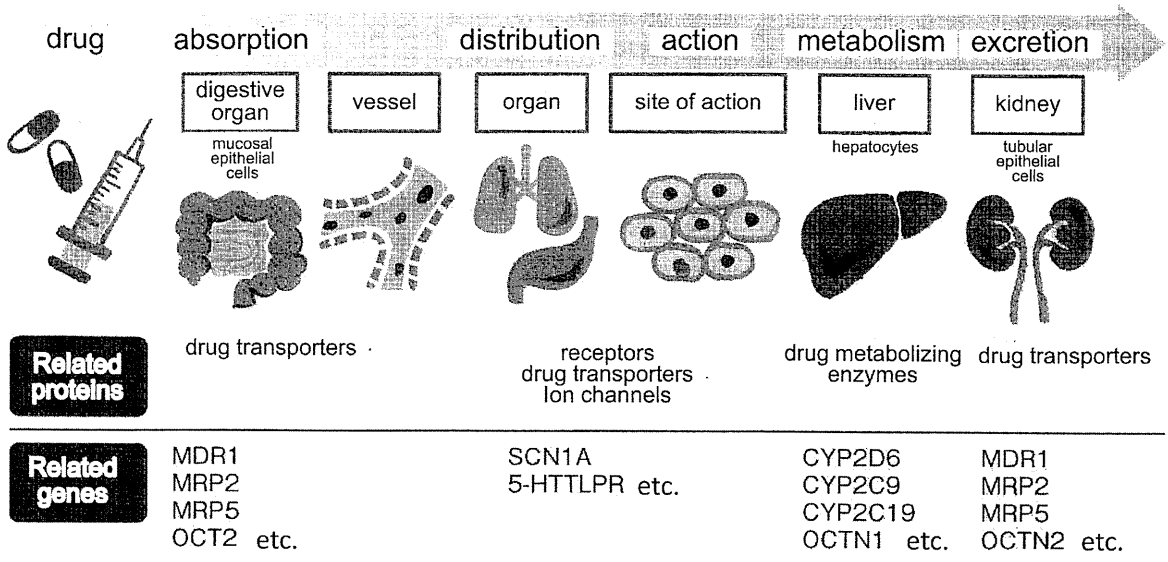


**Fig. 3** Pharmacokinetics and related genes

もしPGx検査により副作用出現のリスクが高いと考えられても，他の選択肢はなく，その薬を使わざるを得ない場合がある．その場合には，副作用出現のための細やかなチェックをしつつ，副作用出現を未然に防ぐことが必要となる．臨床研究の積み重ねによって薬理遺伝学の診療は発展をする．現在，PGx検査においては研究的要素を含みながら診療に応用していくプロセスにある．そこには患者本人と家族に対して，十分な理解を得られるような説明が必要である．生殖細胞系列のゲノムの多型を見る検査が含まれることを認識し，メンデル遺伝を示す疾患の原因遺伝子が薬理遺伝学の対象となり得ることも知っておく必要がある．オーダーメイド医療の対象者への説明と，状況によっては遺伝カウンセリングが必要となる．

### 3. 遺伝情報の取扱い

UNESCOの「ヒト遺伝情報に関する国際宣言(2003)」[10]第14条では，「プライバシー及び機密性」として，個人を特定できるヒト遺伝情報，ヒトのプロテオーム情報及び生物学的試料は(中略)第三者，特に雇用主，保険会社，教育機関及び家族に対して開示，若しくは入手可能とすべきではない．ヒト遺伝情報，ヒトのプロテオーム情報及び生物学的試料を使用する研究に参加する個人のプライバシーは保護され，これらの情報は機密情報として取扱われるべきである」と述べられている．厚生労働省「医療・介護関係事業者における個人情報の適切な取扱いのためのガイドライン(2004)」[11]にも「これが漏えいした場合には，本人及び血縁者が被る被害及び苦痛は大きなものとなるおそれがある．したがって，検査結果及び血液等の試料の取扱いについては，UNESCO国際宣言，医学研究分野の関連指針及び関連団体等が定めるガイドラインを参考とし，特に留意する必要がある．」とされている．一方で，PGx検査の臨床現場における普及により，薬剤の副作用の出現予測や薬剤必要量の予測が可能となった．被検者の薬物治療において，遺伝子情報であるPGx検査結果を医師，看護師，薬剤師，臨床検査技師などが共有することで，副作用の出現を防ぎ，適正量を投与するオーダーメイド医療がなされる．遺伝情報ならば何もかも厳重なセキュリティーの下に置かなければならないとすると，むしろ弊害が出現することになる．遺伝情報の内容に合わせた適切なレベルの取扱いが求められる．

1) 電子カルテの利点と欠点

1999年に厚生省（当時）は診療録の電子媒体による保存を認める通達を出し，2001年には厚生労働省が「保健医療分野の情報化に向けてのグランドデザイン」を策定し，「経済財政諮問会議」は，医療情報システムの構築において，医療サービスのIT化(電子カルテ・レセプト電算処理システムの推進）を決定した．それを受けて，全国の医療機関は，電子カルテを臨床現場に導入し，総合医療管理システムとして発展させている．カルテ記載を電子化することは多くの利点があり，カルテの紛失がないこと，文字の巧緻，拙劣の差がなく判読不能なことがなくな

**Table 1** Comparison between medical information, PGx information and genetic information according to the International Declaration on Human Genetic Data (UNESCO) 16 October 2003

| | General medical information | PGx information | Genetic information |
|---|---|---|---|
| Predictive genetic predispositions | ± | + | + |
| Significant impact on the family | − | − | + |
| Containing unknown information | − | + | + |
| Cultural significance | − | − | + |

**Table 2** Standard on handling personal information including genetic testing at TWMU hospital

| Level | Subject | Management |
|---|---|---|
| A | Monogenic disorders<br>Chromosomal abnormalities<br>Polygenic disorders<br>Susceptivility genetic testing | Genetic counseling is obligatory<br>Limitated access to records and electronic medical records |
| B | Pharmacogenomics (PGx)<br>Pharmacogenetics | Request for written IC by attending doctor<br>Arrange genetic counseling with clinical genetisist, when needed<br>Unlimited access for medical staff to records electronic medical records |
| C | Characterization of cancer cells<br>Somatic cells genetic testing<br>Infection (bacteria and viral examination) | Written IC: leave to the discretion of attending doctor<br>Can leave as general medical information on electronic medical records |
| X | Character, mental state, violence, motor ability, identity of person, parentage test, racial or ancestory derivation | Not subject to medical services |

ること，院内のネットワーク化により任意の場所でカルテを参照できること，検査結果や画像をデータ処理できることなどが挙げられる．それに対して，紙カルテに劣る面のひとつとして，セキュリティーへの配慮の必要性が高いことが挙げられ，この点が，遺伝情報を電子カルテに載せることへの躊躇の理由となっている．

2）電子カルテにおける遺伝情報の取扱い

薬理遺伝学的検査（PGx 検査）の臨床現場における普及により，薬剤の副作用の出現予測や薬剤必要量の予測が可能となった．被検者の薬物治療において，遺伝子情報である PGx 検査結果を医師，看護師，薬剤師，臨床検査技師などが共有することで，副作用の出現を防ぎ，適正量を投与するオーダーメイド医療がなされる．遺伝子情報ならば，何もかも厳重なセキュリティーの下に置かなければならないとすると，むしろ弊害が出現することになる．Table 1 に示すように，薬理遺伝学的検査は単一遺伝子病の遺伝情報ほど特別な地位のものではないが，非遺伝的検査よりは高い基準の配慮が求められる．

このような背景の下に，東京女子医科大学病院では，Table 2 のように遺伝子情報を階層化して，その取扱いレベルを決めた[12]．高いアクセス制限を要するレベル（レベル A，B）では，遺伝子情報サーバーに遺伝子検査データを格納し，ID とパスワードにてアクセスする権限を定めた．単一遺伝子病，染色体検査などの患者本人の確定診断はレベル A とした．保因者診断，発症前診断は将来的にはレベル A の中でさらに高いアクセス制限とする計画であるが，その設定がなされるまでは遺伝子医療センターにおける紙カルテの管理としている．PGx 検査の結果は遺伝子情報サーバーに格納する一方で，そのアクセスは医師，看護師，薬剤師，臨床検査技師など職種により可能とした（レベル B）．さらに，白血病やがん細胞における遺伝子発現などの細胞特性を調べる体細胞遺伝子検査については，遺伝子情報サーバーには格納せず通常の医療情報と同等の扱いとしている（レベル C）．

### 4. 遺伝子医療に携わる人材育成

自分が発症するか（発症前診断），自分は発症しないが保因者であるか（保因者診断），妊娠中の胎児がある疾患に罹患しているか（出生前診断）などに関する遺伝カウンセリングにおいて，また，パーソナルゲノム時代ともいえる個の医療，オーダーメイド医療を診療の場に導入すべき状況を迎えるにあたって，臨床遺伝学の専門的教育と，遺伝カウンセリング教育が必要である．医師においては，被検者の心理状態をつねに把握しながら遺伝子医療，遺伝カウ

ンセリングを実施する資格として，臨床遺伝専門医（日本人類遺伝学会と日本遺伝カウンセリング学会の共同認定）の養成が行われている．非医師の職種としては，上記二学会の共同認定の認定遺伝カウンセラー養成が大学院教育としてなされている．本学遺伝子医療センターでは大学院医学研究科先端生命医科学系専攻遺伝子医学分野において遺伝カウンセラー養成コースを設けて，臨床遺伝専門医の教育と共に，遺伝医療，遺伝教育，さらに企業において活躍する認定遺伝カウンセラーとしての人材育成を実施している．遺伝カウンセリングでは，本人・家族・血縁者に対して，生活設計上の選択を自らの意思で決定し行動できるよう臨床遺伝学的診断を行い，遺伝医学的判断に基づき遺伝予後などの適切な情報を提供し支援する．患者・家族と遺伝カウンセリング担当者との良好な信頼関係に基づき，さまざまなコミュニケーションが行われ，この過程で医療的心理的精神的援助がなされる．一方的な医学情報提供だけではないことに留意すべきである．

## おわりに

ゲノム解析研究が実を結び，多くの疾患の正確な診断と根本治療へのプロセスを現在，我々は歩んでいる．高度医療の臨床応用の過程において大切なことは，遺伝子医学というハード面と，その医療を受ける患者，家族への情報提供，支援というソフト面である．患者，家族の人権および，生命の尊厳への慎重な配慮が求められる．遺伝子診療が実地医療の一部となりつつある現在，遺伝カウンセリングの必要性は増しており，生命倫理，医療倫理，社会倫理に関する十分な教育と人材育成がなされることが重要である．

## 文　献


1) **Schuster SC**: Next-generation sequencing transforms today's biology. Nat Methods **5**: 16–18, 2008
2) **Human Genetics Commission**: More Genes Direct: A report on developments in the availability, marketing and regulation of genetic tests supplied directly to the public. (2007) http://www.hgc.gov.uk/UploadDocs/DocPub/Document/More%20Genes%20Direct%20-%20final.pdf (accessed on Sept. 1, 2011)
3) **日本人類遺伝学会**：「DTC 遺伝学的検査に関する見解」2008 年 10 月 2 日　http://jshg.jp/dtc/index.html（参照 2011 年 9 月 1 日）
4) **遺伝医学関連学会**：「遺伝学的検査に関するガイドライン（2003）」http://jshg.jp/resources/data/10academies.pdf（参照 2011 年 9 月 1 日）
5) **日本医学会**：「医療における遺伝学的検査・診断に関するガイドライン（2011）」http://jams.med.or.jp/guideline/genetics-diagnosis.pdf（参照 2011 年 9 月 1 日）
6) **Bennett RL, Steinhaus KA, Uhrich SB et al**: Recommendations for standarardized human pedigree nomenclature. Am J Hum Genet **56**: 745–752, 1995
7) Guidance for Industry E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories by FDA, 2008
8) **Chen P, Lin JJ, Lu CS et al**: Carbamazepine-induced toxic effects and HLA-B＊1502 screening in Taiwan. N Engl J Med **364**: 1126–1133, 2011
9) **Minami H, Sai K, Saeki M et al**: Irinotecan pharmacokinetics/pharmacodynamics and *UGT1A1*＊6 and ＊28. Pharmacogenet Genomics **17**: 497–504, 2007
10) **UNESCO**：「ヒト遺伝情報に関する国際宣言（2003）」http://portal.unesco.org/en/ev.php-URL_ID=17720&URL_DO=DO_TOPIC&URL_SECTION=201.html（参照 2011 年 9 月 1 日）
11) **厚生労働省**：「医療・介護関係事業者における個人情報の適切な取扱いのためのガイドライン（2004）」http://www.mhlw.go.jp/houdou/2004/12/h1227-6.html（参照 2011 年 9 月 1 日）
12) **福島武春，斎藤加代子，菅野　仁ほか**：遺伝子検査結果の電子化．日本遺伝カウンセリング学会誌 **31**：131–135, 2011

J Epidemiol 2011;21(3):211-216
doi:10.2188/jea.JE20100149

Short Communication

# How Can the National Burden of Parkinson's Disease Comorbidity and Mortality Be Estimated for the Japanese Population?

Yuriko Doi[1], Tetsuji Yokoyama[2], Yoshikazu Nakamura[3], Masaki Nagai[4], Kenichi Fujimoto[5], and Imaharu Nakano[5]

[1]Department of Education and Training Technology, National Institute of Public Health, Saitama, Japan
[2]Department of Human Resources Development, National Institute of Public Health, Saitama, Japan
[3]Department of Public Health, Jichi Medical University School of Medicine, Tochigi, Japan
[4]Department of Public Health, Saitama Medical University, Saitama, Japan
[5]Division of Neurology, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan

Received October 8, 2010; accepted December 22, 2010; released online March 12, 2011

## ABSTRACT

**Background:** Good medical care results in long survival for patients with Parkinson's disease (PD). However, little is known about the burden of PD comorbidity and mortality in Japan. This is the first study to examine comorbid diseases of PD decedents and extrapolate PD death rates from multiple-cause coding mortality data for the total population of Japan.

**Methods:** Data for 4589 certified deaths due to PD as the underlying cause of death (ICD-10 code: G20) were obtained from the 2008 Japanese vital statistics. Of those, comorbidities listed in the death certificates of 477 randomly selected decedents were analyzed. All diseases or conditions mentioned on death certificates were counted and ranked in descending order of frequency. The death rates (per 100 000 population) from PD were calculated using Japanese National Vital Statistics. The estimated rate of deaths with PD was extrapolated using US death data from a multiple-cause coding system, as no such system is available in Japan, with adjustment for the difference in disease structure between countries.

**Results:** Average age at death was 80.9 years. The top 5 comorbid diseases ranked as contributory causes of death were cerebrovascular diseases (4.0%), dementia (3.8%), diabetes mellitus (3.6%), malignant neoplasm (2.5%), and heart diseases (2.3%). Overall, the death rates from and with PD were 3.6 and 5.8, respectively.

**Conclusions:** Analysis restricted to data from the underlying-cause coding system underestimated the national burden of PD comorbidity and mortality. Use of death certificates and multiple-cause mortality data complement the existing system.

***Key words:*** Parkinson's disease; comorbidity; mortality; causes of death; Japan

## INTRODUCTION

Under the Statistics Act of Japan, the Japanese Ministry of Health, Labour and Welfare is charged with overseeing the annual collection of vital statistics surveys to analyze vital events and obtain a basic population data source for policy making on health, labor, and welfare.[1] The procedures adhere to international standards for mortality statistics regarding underlying cause of death, which is defined by the World Health Organization as the disease or injury that initiated the train of morbid events leading directly to death or the circumstances of the accident or violence that produced the fatal injury.[2] Coders select underlying causes of deaths in accordance with the rules and guidelines on coding for deaths and diseases.[3] Overall, underlying cause of death data are reported to capture approximately 90% of deaths mentioned in the death certificates for malignant neoplasms.[4–8] Statistics on underlying cause of death can be valuable in describing types of death for which a single primary cause is clinically considered to contribute.

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the 4 cardinal motor signs of tremor at rest, bradykinesia, rigidity, and postural instability, and by other non-motor clinical manifestations. Average age at onset is approximately 55 years. With the development of various kinds of treatments, the average age at

Address for correspondence. Yuriko Doi, Department of Education and Training Technology, National Institute of Public Health, 2-3-6 Minamai, Wako, Saitama 351-0197, Japan (e-mail: yuriko@niph.go.jp).
Copyright © 2011 by the Japan Epidemiological Association

death of patients with PD is now close to that of the general population. Because the disease is incurable, patients survive for a long period, often decades, under medical supervision.[9]

As with other chronic diseases, the causes of PD death are more likely to represent a number of co-existing conditions among which there may be no direct etiologic chain to facilitate the identification of a single underlying cause. To complement statistics on underlying cause of death, statistics encompassing multiple causes of death have been introduced as standard practice in a number of Western countries. Analysis of multiple cause of death revealed that data on underlying cause of death represent only 30% to 50% of deaths with PD mentioned in death certificates.[4,8,10] How can we estimate the national burden of PD comorbidity and mortality without a multiple-cause coding system for mortality statistics in Japan? The present study is the first to examine comorbid diseases of decedents from PD using their death certificates and to extrapolate PD death rates from multiple-cause coding mortality data.

## METHODS

### Data

#### *Death certificates*

There were 4589 Japanese decedents for whom PD was the underlying cause of death in the 2008 vital statistics. To analyze these death certificates, a random sample of decedents was selected, with a 10% probability for each prefecture. There were no significant differences in demographic characteristics between the vital statistics dataset and the sampled death certificates (Table 1).

Two of the authors (YD and TY) are medical epidemiologists and transcribed all mentioned causes of death from the copied death certificates of the sampled decedents, after obtaining permission to do so from the Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare, Japan. The transcribed information did not contain any personally identifiable information. Based on standard clinical practice, one author (YD), who has more than 10 years of experience in clinical medicine, classified all mentioned causes of death other than PD into several categories of diseases and medical conditions. The present study was approved in March 2010 by the Institutional Review Board of the National Institute of Public Health, Japan.

#### *Vital statistics*

Data for 4589 decedents from PD as the underlying cause of death were extracted from the national mortality database of vital statistics, after obtaining permission from the Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare, Japan. The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) uses the code G20 for PD.[2,11] The data used in the present study did not contain any personally identifiable information.

**Table 1. Demographic characteristics of decedents for whom Parkinson's disease was listed as the underlying cause of death on death certificates (Japan, 2008)**

| Characteristics | All decedents ($n$ = 4589) | | Sampled decedents[a] ($n$ = 477) | |
|---|---|---|---|---|
| | Number or Mean | % or SD | Number or Mean | % or SD |
| Sex | | | | |
| Men | 2124 | 46.3 | 208 | 43.6 |
| Women | 2465 | 53.7 | 269 | 56.4 |
| Age[b] | | | | |
| Men | 79.5 | 7.2 | 80.1 | 7.2 |
| Women | 82.0 | 7.3 | 82.7 | 6.9 |
| Both | 80.9 | 7.4 | 81.6 | 7.1 |
| Marital status | | | | |
| Married | 2380 | 51.9 | 239 | 50.1 |
| Single | 184 | 4.0 | 21 | 4.4 |
| Bereaved | 1865 | 40.6 | 200 | 41.9 |
| Separated | 158 | 3.4 | 17 | 3.6 |
| Unknown | 2 | 0.0 | 0 | 0.0 |
| Occupation | | | | |
| Farming | 349 | 7.6 | 48 | 10.1 |
| Self-employed | 242 | 5.3 | 31 | 6.5 |
| Employed | 570 | 12.5 | 60 | 12.5 |
| Other | 302 | 6.6 | 29 | 6.1 |
| Unemployed | 2718 | 59.2 | 266 | 55.8 |
| Unknown | 408 | 8.9 | 43 | 9.0 |
| Place of death | | | | |
| Hospital | 3496 | 76.2 | 363 | 76.1 |
| Clinic | 156 | 3.4 | 11 | 2.3 |
| Healthcare facility for the aged | 103 | 2.2 | 15 | 3.1 |
| Nursing home | 325 | 7.1 | 33 | 6.9 |
| Home | 466 | 10.2 | 48 | 10.1 |
| Other | 43 | 0.9 | 7 | 1.5 |

[a]Sampled decedents were randomly selected with a 10% probability from all deaths attributed to Parkinson's disease, by prefecture, in 2008.
[b]Values are means and standard deviations (SDs).

### Statistical analysis

#### *Analysis of death certificates*

All categorized causes or conditions mentioned, other than PD, in death certificates of the sampled decedents were counted and ranked in descending order of frequency as 1 of 3 types of causes: immediate, intermediate, or contributory. An immediate cause is a final disease or condition resulting in death and is described on the top line in Part (I) of the death certificate. Intermediate causes are diseases, injuries, or complications (other than immediate cause) in the chain of events that directly caused the death and are described in Part (I) of the death certificate. Contributory causes are other significant conditions that contributed to the causes described in Part (I), but did not directly result in those causes. Contributory causes are described in Part (II) of the death certificate.[12]

#### *Analysis of vital statistics*

The number and rate of deaths in individuals for whom PD was listed as the underlying cause of death were calculated according to 5-year age intervals using the Japanese national

vital statistics and data on the Japanese population for the year 2008. Currently, there is no multiple-cause coding system in Japan; however, the US Centers for Disease Control and Prevention (CDC) publically releases data on multiple cause-of-death. Therefore, we calculated the number and rate of PD as a multiple cause of death according to sex and age group by weighting the underlying cause of death data from the Japanese national vital statistics in 2008 with multiple cause of death data from publically available US national vital statistics in 2006 (see Appendix).[13] The equations, (1)–(3), are as follows: $P_{JAPAN,j}(G20|D_i)$ is the proportion of death certificates mentioned with PD to those for $D_i$ as the underlying cause of death from disease $i$ in the $j$-th sex-age-group in Japan; $D_i$ is ischemic heart disease (ICD-10: I20–I25), malignant neoplasm (C00–C75), cerebrovascular disease (I60–I69), pneumonia (J10–J18), PD (G20), or other (all other codes). The same is true for $P_{US,j}(G20|D_i)$. $P_{JAPAN,j}(G20|D_i) = 1$ when $D_i$ is G20. Otherwise, equation (1) can be used: (1) $P_{JAPAN,j}(G20|D_i) = P_{US,j}(G20|D_i) \times \frac{R_{JAPAN,j}}{R_{US,j}}$, where $R_{JAPAN,j}$ and $R_{US,j}$ are the death rates from PD as the underlying cause of death in the $j$-th sex-age-group in Japan and the United States, respectively. Equation (1) is used to adjust for the difference in disease structure between the 2 countries.

Then, the number of multiple-cause deaths from PD in the death certificate with $D_i$ as the underlying cause of death in the $j$-th sex-age-group, $M_{i,j}$, is estimated as: (2) $M_{i,j} = N_{i,j} \times P_{JAPAN,j}(G20|D_i)$, where $N_{i,j}$ is the number of the underlying cause of death from $D_i$ in the $j$-th sex-age-group. The number of the multiple cause of death from PD in the $j$-th sex-age-group, $M_j$, is obtained by summing $M_{i,j}$ for all underlying causes of death as: (3) $M_j = \sum_i M_{i,j}$. The sex- and age-specific rates of multiple-cause of deaths from PD were calculated by dividing $M_j$ by the corresponding sex- and age-specific Japanese population for the year 2008. The multiple cause of death rates, by sex and in total, were calculated from the corresponding numbers of summed multiple-cause deaths and populations.

## RESULTS

Mean age at death among PD decedents was 79.5 years for men, which exceeded the average life expectancy of men in the general population (79.3 years), and 82.0 years for women, which was lower than that of women in the general population (86.1 years; Table 1).

Table 2 shows all causes or conditions mentioned, other than PD, in the death certificates of 477 decedents. The 5 most frequent comorbid diseases listed as contributory causes of death were cerebrovascular diseases, dementia, diabetes mellitus, malignant neoplasm, and heart diseases. The most common immediate or intermediate cause of death was aspiration or suffocation that caused pneumonia, respiratory failure, or multiple organ failure leading to death.

Table 3 shows the death rates per 100 000 population according to underlying and multiple cause of death. Both rates increased with age, from 0.5 and 0.7, respectively, in those aged 55 to 64 years to 40.8 and 71.3 in those aged 85 years or older. The overall death rate estimated from extrapolation of US data on multiple-cause deaths was approximately 1.6 times that obtained from Japanese data on underlying cause of death: 5.8 versus 3.6, respectively.

## DISCUSSION

### Death certificate analysis

Our most noteworthy finding was that dementia and diabetes mellitus appeared together with the 3 leading causes of death—cerebrovascular disease, malignant neoplasm and heart disease—as comorbid diseases in a representative sample of the Japanese PD population. Because our analysis was able to detect chronic diseases and conditions that, while not fatal by themselves, could contribute to causing death, diabetes mellitus was highly ranked in our death certificate analysis, even though it is not among the 10 leading causes of death in the underlying-cause coding system of Japanese vital statistics. Much the same was true for dementia. Dementia is a major long-term cause of disability in people with PD and is reported in 30% to 80% of individuals with PD.[14] The value observed in the present study, 4.8%, was quite low. This difference between studies may be due to differences in methods. The high prevalence of dementia in PD patients was mostly reported in clinical studies of PD patients who had undergone comprehensive neuropsychological assessment. Oral health, which is important in PD,[15] was not mentioned anywhere in the death certificates of the present study.

Death certificate analysis has limitations. First, there is no multiple-cause coding system in Japan. Therefore, it was impossible to obtain death certificates in which PD was mentioned, but was not the underlying cause of death, from the 1.14 million death certificates filed in 2008. It may also be that parts of the analyzed death certificates were incomplete or inaccurate because of the possibility that (1) contributory causes are disregarded in data on underlying cause of death in national mortality statistics, (2) detailed medical records are sometimes unavailable at death, especially for decedents with long periods of morbidity, and (3) physicians sometimes have difficulty in reporting detailed medical information on the death certificates of such decedents.

### Analysis of vital statistics

The present study showed that analysis restricted to data on underlying cause of death underestimates PD mortality in Japan. Our estimated number of PD decedents was nearly 60% higher than the number of decedents due to PD as the underlying cause of death.

**Table 2. All causes or conditions mentioned, other than Parkinson's disease, in death certificates of 477 decedents randomly selected from 4589 deaths due to Parkinson's disease as the underlying cause of death (Japan, 2008)**

| Immediate causes[a] | Number | % | Intermediate causes[b] | Number | % | Contributory causes[c] | Number | % |
|---|---|---|---|---|---|---|---|---|
| Aspiration or suffocation | 106 | 22.2 | Aspiration or suffocation | 64 | 13.4 | Cerebrovascular diseases | 19 | 4.0 |
| Pneumonia | 70 | 14.7 | Senile deterioration | 8 | 1.7 | Dementia | 18 | 3.8 |
| Respiratory failure | 61 | 12.8 | Pneumonia | 8 | 1.7 | Diabetes mellitus | 17 | 3.6 |
| Senile deterioration | 52 | 10.9 | Dementia | 5 | 1.0 | Malignant neoplasms | 12 | 2.5 |
| Heart diseases | 30 | 6.3 | Cerebrovascular diseases | 4 | 0.8 | Heart diseases | 11 | 2.3 |
| Multiple organ failure | 12 | 2.5 | Respiratory failure | 4 | 0.8 | Lung diseases | 10 | 2.1 |
| $CO_2$ narcosis or hypoxemia | 9 | 1.9 | Lung diseases | 3 | 0.6 | Infection, sepsis or DIC | 8 | 1.7 |
| Infection, sepsis or DIC | 5 | 1.0 | Heart diseases | 3 | 0.6 | Hypertension or hypotension | 8 | 1.7 |
| Renal diseases | 3 | 0.6 | Neuroleptic malignant syndrome | 2 | 0.4 | Diseases of the gastrointestinal tract | 8 | 1.7 |
| Lung diseases | 2 | 0.4 | Mental disorders | 2 | 0.4 | Fracture | 6 | 1.3 |
| Neuroleptic malignant syndrome | 2 | 0.4 | Infection, sepsis or DIC | 2 | 0.4 | Connective tissue diseases | 6 | 1.3 |
| Cerebrovascular diseases | 2 | 0.4 | Disuse syndrome | 2 | 0.4 | Diseases of arteries or arterioles | 4 | 0.8 |
| Diseases of the gastrointestinal tract | 1 | 0.2 | Diseases of the gastrointestinal tract | 2 | 0.4 | Senile deterioration | 4 | 0.8 |
| Disuse syndrome | 1 | 0.2 | $CO_2$ narcosis or hypoxemia | 2 | 0.4 | Pneumonia | 4 | 0.8 |
| Unknown | 1 | 0.2 | Renal diseases | 1 | 0.2 | Mental disorders | 4 | 0.8 |
| | | | Hypertension or hypotension | 1 | 0.2 | Lung diseases | 4 | 0.8 |
| | | | Diabetes mellitus | 1 | 0.2 | Disuse syndrome | 4 | 0.8 |
| | | | Decubitus ulcer | 1 | 0.2 | Aspiration or suffocation | 3 | 0.6 |
| | | | Anemia or hypoalbuminemia | 1 | 0.2 | Liver diseases | 3 | 0.6 |
| | | | | | | Decubitus ulcer | 3 | 0.6 |
| | | | | | | Respiratory failure | 1 | 0.2 |
| | | | | | | Anemia or hypoalbuminemia | 1 | 0.2 |

Abbreviation: DIC, disseminated intravascular coagulation.
[a]An immediate cause is a final disease or condition resulting in death, described on the top line in Part (I) of the death certificate.
[b]Intermediate causes are diseases, injuries, or complications, other than immediate causes, in the chain of events that directly cause death, as described in Part (I) of the death certificate.
[c]Contributory causes are other significant conditions that contribute to the causes cited in Part (I), but do not directly result in those causes; they are described in Part (II) of the death certificate.

**Table 3. Number and rate of Parkinson's disease deaths, based on national vital statistics, by sex and age group (Japan, 2008): Underlying cause of death versus multiple cause of death**

| Age (years) | Underlying cause of death | | | | | | Multiple cause of death[a] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number of deaths | | | Rate per 100 000 population | | | Estimated number of deaths | | | Estimated rate per 100 000 population | | |
| | Men | Women | Total | Men | Women | Total | Men | Women | Total | Men | Women | Total |
| 0–14 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 |
| 15–24 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 |
| 25–34 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 |
| 35–44 | 2 | 1 | 3 | 0.0 | 0.0 | 0.0 | 2 | 2 | 4 | 0.0 | 0.0 | 0.0 |
| 45–54 | 6 | 7 | 13 | 0.1 | 0.1 | 0.1 | 9 | 10 | 19 | 0.1 | 0.1 | 0.1 |
| 55–64 | 53 | 32 | 85 | 0.6 | 0.3 | 0.5 | 83 | 45 | 128 | 0.9 | 0.5 | 0.7 |
| 65–74 | 381 | 297 | 678 | 5.4 | 3.7 | 4.5 | 623 | 407 | 1030 | 8.8 | 5.1 | 6.9 |
| 75–84 | 1187 | 1214 | 2401 | 29.4 | 21.2 | 24.6 | 2023 | 1769 | 3792 | 50.1 | 30.9 | 38.8 |
| 85+ | 495 | 914 | 1409 | 52.4 | 36.4 | 40.8 | 911 | 1549 | 2461 | 96.5 | 61.8 | 71.3 |
| Total | 2124 | 2465 | 4589 | 3.4 | 3.8 | 3.6 | 3652 | 3782 | 7434 | 5.9 | 5.8 | 5.8 |

[a]The estimated number and rate of multiple-cause PD deaths were calculated according to sex and age group by weighting data on underlying cause of death from 2008 Japanese national vital statistics with multiple cause of death data from publically available 2006 US national vital statistics (see reference 13).

In the equation used in the present study, the estimates were adjusted for differences in disease structure between the United States and Japan. However, this adjustment could not fully account for racial differences between populations in vulnerabilities and comorbidities regarding PD. Age-standardized PD prevalence and incidence are lower in Japanese studies than in US studies.[16] The underlying cause of death as a percentage of multiple cause of death reports was 49% in the US population in 2000–2001 and 56% in the UK population in 2001–2006.[4,10] It remains to be seen

**Appendix. Number and rate of deaths with Parkinson's disease mentioned on death certificates, by sex and age group (United States, 2006): Underlying cause of death versus multiple cause of death**

| Age (years) | Underlying cause of death | | | | | | Multiple cause of death | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number of deaths | | | Rate per 100 000 population | | | Number of deaths | | | Rate per 100 000 population | | |
| | Men | Women | Total | Men | Women | Total | Men | Women | Total | Men | Women | Total |
| 0–14 | 0 | 1 | 1 | 0.0 | 0.0 | 0.0 | 0 | 2 | 2 | 0.0 | 0.0 | 0.0 |
| 15–24 | 0 | 1 | 1 | 0.0 | 0.0 | 0.0 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 |
| 25–34 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 | 3 | 0 | 0 | 0.0 | 0.0 | 0.0 |
| 35–44 | 4 | 1 | 5 | 0.0 | 0.0 | 0.0 | 4 | 4 | 0 | 0.0 | 0.0 | 0.0 |
| 45–54 | 36 | 16 | 52 | 0.2 | 0.1 | 0.1 | 67 | 30 | 97 | 0.3 | 0.1 | 0.2 |
| 55–64 | 251 | 130 | 381 | 1.7 | 0.8 | 1.2 | 450 | 239 | 689 | 3.0 | 1.5 | 2.2 |
| 65–74 | 1512 | 783 | 2295 | 17.4 | 7.6 | 12.1 | 2677 | 1359 | 4036 | 30.9 | 13.3 | 21.3 |
| 75–84 | 5517 | 3544 | 9061 | 104.1 | 45.7 | 69.5 | 9665 | 6147 | 15812 | 182.4 | 79.3 | 121.2 |
| 85+ | 3894 | 3741 | 7635 | 230.7 | 103.7 | 144.1 | 6860 | 6809 | 13669 | 406.3 | 188.7 | 258.1 |
| Total | 11214 | 8217 | 19431 | 7.6 | 5.4 | 6.5 | 19726 | 14590 | 34316 | 13.4 | 9.6 | 11.5 |

Note: The data source is multiple cause of death data from publically available US national vital statistics (see reference 13).

whether these percentages are accurate for the Japanese population.

### Epidemiological implications

To estimate more accurately the national burden of PD comorbidity and mortality, a multidimensional approach is also required for the Japanese population. This approach is not a substitute for, but rather an extension of, existing data on underlying cause of death,[5,17,18] and has already been adopted in the United States, the United Kingdom, Sweden, Spain, and France.[17–21] The addition of this multiple-cause coding system to the current Japanese system would be an ideal long-term solution. It should also be recognized that, in a multiple-cause coding system, certain epidemiological catchment areas should be designated for the regular collection and release of necessary reference data on comorbidity and mortality statistics. Most importantly, it is essential to maintain the quality of death certificates by enhancing understanding of their importance in the fields of medicine, public health, and health policy.[5–7]

### Conclusion

The present study showed that analysis using only data from the underlying-cause coding system underestimated the national burden of PD comorbidity and mortality. Use of death certificates and multiple-cause mortality data are thus desirable complements to the existing system.

## ACKNOWLEDGMENTS

This study was supported by grants from Health and Labour Sciences Research of the Ministry of Health, Labour and Welfare, Japan: Research Committee on Epidemiology of Intractable Diseases and Research Committee on CNS Degenerative Diseases of Intractable Diseases.

Conflicts of interest: None declared.

## REFERENCES

1. Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare, Japan. Vital statistics of Japan 2008 volume 1. Tokyo: Statistics and Information Department, Ministry of Health, Labour and Welfare, Japan; 2010 (in Japanese).
2. Geneva: World Health Organization [cited 2010 Aug 25]. Available from http://www.who.int/healthinfo/statistics/mortdata/en/.
3. Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare, Japan. Rules and guidelines on coding the causes of deaths and diseases. In: International statistical classification of diseases and related health problems, tenth revision: ICD-10. Tokyo: Health and Welfare Statistics Association; 2004. p. 50–151 (in Japanese).
4. Redelings MD, Sorvillo F, Simon P. A comparison of underlying cause and multiple causes of death: US vital statistics, 2000–2001. Epidemiology. 2006;17:100–3.
5. Israel RA, Rosenberg HM, Curtin LR. Analytical potential for multiple cause-of-death data. Am J Epidemiol. 1986; 124:161–79.
6. Chamblee RF, Evans MC. New dimensions in cause of death statistics. Am J Public Health. 1982;72:1265–70.
7. Dorn HF, Moriyama IM. Uses and significance of multiple cause tabulations for mortality statistics. Am J Public Health Nations Health. 1964;54:400–6.
8. Goldacre MJ, Duncan ME, Cook-Mozaffari P, Griffith M. Trends in mortality rates comparing underlying-cause and multiple-cause coding in an English population 1979–1998. J Public Health Med. 2003;25:249–53.
9. Disease Prevention Study Group. Parkinson's disease. In: Disease Prevention Study Group, editor. Guidelines of diagnoses and treatments for intractable diseases. 3rd ed. Tokyo: Tokyo Roppo Publishing; 2005. p. 249–69 (in Japanese).
10. Goldacre MJ, Duncan M, Griffith M, Turner MR. Trends in death certification for multiple sclerosis, motor neuron disease, Parkinson's disease and epilepsy in English populations 1979–2006. J Neurol. 2010;257:706–15.

11. Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare, Japan. Vital statistics of Japan 2008 volume 2. Tokyo: Statistics and Information Department, Ministry of Health, Labour and Welfare, Japan; 2010 (in Japanese).
12. Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare, Japan. Manual to fill in a death certificate. Available from http://www.mhlw.go.jp/toukei/manual/dl/manual.pdf (in Japanese).
13. Atlanta: Centers for Disease Prevention and Control, the United States of America [cited 2010 Aug 13]. Available from http://wonder.cdc.gov/.
14. Obeso JA, Rodriguez-Oroz MC, Goetz CG, Marin C, Kordower JH, Rodriguez M, et al. Missing pieces in the Parkinson's disease puzzle. Nat Med. 2010;16:653–61.
15. Nakayama Y, Washio M, Mori M. Oral health conditions in patients with Parkinson's disease. J Epidemiol. 2004;14:143–50.
16. Muangpaisan W, Hori H, Brayne C. Systematic review of the prevalence and incidence of Parkinson's disease in Asia. J Epidemiol. 2009;19:281–93.
17. Goodman RA, Manton KG, Nolan TF Jr, Bregman DJ, Hinman AR. Mortality data analysis using a multiple-cause approach. JAMA. 1982;247:793–6.
18. Weed JA. Vital statistics in the United States: preparing for the next century. Popul Index. 1995;61:527–39.
19. Lindahl BI, Johansson LA. Multiple cause-of-death data as a tool for detecting artificial trends in the underlying cause statistics: a methodological study. Scand J Soc Med. 1994;22:145–58.
20. Tardon AG, Zaplana J, Hernandez R, Cueto A. Usefulness of the codification of multiple causes of death in mortality statistics. Int J Epidemiol. 1995;24:1132–7.
21. Romon I, Jougla E, Balkau B, Fagot-Campagna A. The burden of diabetes-related mortality in France in 2002: an analysis using both underlying and multiple causes of death. Eur J Epidemiol. 2008;23:327–34.

Asari et al. BMC Neurology 2011, 11:35
http://www.biomedcentral.com/1471-2377/11/35

BMC Neurology

RESEARCH ARTICLE Open Access

# Subregional 6-[$^{18}$F]fluoro-L-*m*-tyrosine Uptake in the Striatum in Parkinson's Disease

Sayaka Asari[1*], Ken-ichi Fujimoto[1], Akihiro Miyauchi[2], Toshihiko Sato[3], Imaharu Nakano[1] and Shin-ichi Muramatsu[1*]

**Abstract**

**Background:** In idiopathic Parkinson's disease (PD) the clinical features are heterogeneous and include different predominant symptoms. The aim of the present study was to determine the relationship between subregional aromatic l-amino acid decarboxylase (AADC) activity in the striatum and the cardinal motor symptoms of PD using high-resolution positron emission tomography (PET) with an AADC tracer, 6-[$^{18}$F]fluoro-L-*m*-tyrosine (FMT).

**Methods:** We assessed 101 patients with PD and 19 healthy volunteers. PD was diagnosed based on the UK Brain Bank criteria by two experts on movement disorders. Motor symptoms were measured with the Unified Parkinson's Disease Rating Scale (UPDRS). FMT uptake in the subregions of the striatum was analyzed using semi-automated software for region-of-interest demarcation on co-registered magnetic resonance images.

**Results:** In all PD patients, FMT uptake was decreased in the posterior putamen regardless of predominant motor symptoms and disease duration. Smaller uptake values were found in the putamen contralateral to the side with more affected limbs. The severity of bradykinesia, rigidity, and axial symptoms was correlated with the decrease of FMT uptake in the putamen, particularly in the anterior part. No significant correlation was observed between tremors and FMT uptake.

**Conclusions:** Decrease of FMT uptake in the posterior putamen appears to be most sensitive in mild PD and uptake in the anterior putamen may reflect the severity of main motor symptoms, except for tremor.

## Background

Cardinal motor symptoms such as bradykinesia, rigidity, and tremor in Parkinson's Disease (PD) become apparent after a depletion of dopamine in the striatum to approximately 20% of normal levels and a reduction in aromatic L-amino acid decarboxylase (AADC) activity to 5%-20% of normal levels [1,2]. In PD, dopaminergic hypofunction in the striatum is not homogenous in association with the selective loss of ventral intermediate and lateral cell groups of the substantia nigra pars compacta that project to the posterior part of the striatum [3], although the reason for this selective vulnerability remains unknown.

Positron emission tomography (PET) is valuable for assessing altered dopamine function in PD. The first tracer used to visualize and assess the integrity of dopamine presynaptic systems was 6-[$^{18}$F]fluoro-L-dopa (FDOPA), a fluoro-analog of L-dopa [4]. FDOPA is taken up into the dopaminergic axon terminals and decarboxylated by AADC before being trapped and stored in synaptic vesicles. FDOPA uptake is highly correlated with viable dopaminergic cells in neurotoxin-lesioned monkeys [5] and in postmortem human PD brains [6]. A shortcoming complicating the use of this agent, however, is that metabolites of FDOPA (such as 3-*O*-methyl-[$^{18}$F]fluoro-L-dopa, which is formed by the action of the ubiquitous enzyme catechol-*O*-methyl-transferase (COMT)) enter the brain and diminish image contrast. An alternative agent is the non-catecholic tracer 6-[$^{18}$F] fluoro -L-*m*-tyrosine (FMT). FMT is also a good substrate for AADC but is not metabolized by COMT; thus, FMT uptake has approximately twice the sensitivity of FDOPA uptake and more fully represents the extent of AADC activity [7-10].

To elucidate the relationship between the main motor symptoms of PD and subregional AADC activity in the striatum, we applied a semi-automated segmentation method for extracting putaminal subregions from

* Correspondence: sasari@jichi.ac.jp; muramats@jichi.ac.jp
[1]Division of Neurology, Department of Medicine, Jichi Medical University, Tochigi, Japan
Full list of author information is available at the end of the article

BioMed Central

© 2011 Asari et al; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

high-resolution FMT PET images that were co-registered with 3.0-tesla magnetic resonance (MR) images.

## Methods

### Subjects and clinical evaluation

Our sample consisted of 101 patients with PD and 19 healthy individuals. PD was diagnosed clinically according to the UK PD Society Brain Bank criteria [11]. All of the patients had bradykinesia and at least one of the three features of PD: 4-6 Hz resting tremor, rigidity, and postural instability. All of the patients had asymmetric onset and showed a positive response to dopaminergic medication. None exhibited atypical symptoms such as severe gaze palsy or symptomatic dysautonomia. The control group included healthy individuals with no history of neurologic or psychiatric diseases.

Motor symptoms were evaluated using the motor examination part of the Unified Parkinson's Disease Rating Scale (UPDRS). Motor subscores were determined as follows: tremor (motor UPDRS: 20 + 21), bradykinesia (motor UPDRS: 23 + 24 + 25 + 26), rigidity (motor UPDRS: 22), and axial (motor UPDRS: 18 + 19 + 27 + 28 + 29 + 30 + 31). The mini-mental state examination (MMSE) was used to assess cognitive function.

This study was approved by the Institutional Ethics Committee of Jichi Medical University and all participants gave written informed consent.

### PET imaging

All patients stopped levodopa at least 16 h before PET. To increase the availability of the tracer, all subjects took 2.5 mg/kg of carbidopa (a peripheral AADC inhibitor) orally 1 h before FMT injection. Prior to the emission scan, a 10 min transmission scan was obtained for attenuation correction. Subsequently, 0.12 mCi/kg of FMT in saline was infused into an antecubital vein and a 30-90 min static three-dimensional acquisition was started simultaneously using a PET-CT (GEMINI GXL, Philips, Amsterdam, The Netherlands). Each subject also underwent 3.0-tesla MR imaging (Achieva 3.0 T, Philips) using an inversion recovery (IR) proton density (PD)-weighted pulse sequence to enhance the contrast of anatomical structures. The PET and MR imaging data were co-registered with a fusion processing program (Syntegra, Philips) to produce fusion images. This program provided manual and point-based image registration as well as automated methods of gray-value-based image registration, including a mutual information algorithm [12]. In addition, an adaptive level set of segmentation was used for coregistration of CT and MRI imaging data [13].

### Semi-automated region of interest analysis

Regions-of-interest (ROIs) in the putamen and caudate nucleus were defined in three dimensions (3-D) bilaterally on the co-registered MR images where the striatum was best visualized. The putamen and the head of caudate nucleus were delineated by manual inspection on the three to five adjacent MR planes that corresponded to those planes on the PET images. The putamen was then automatically divided into three parts in the rostrocaudal direction using dedicated software for ROI demarcation. The 3-D ROIs (volumes of interest, VOIs) were extracted automatically by connecting two-dimensional drawings on each plane using a linear interpolation algorithm for VOI outlines. For reference, cerebellar ROIs were also defined in 3-D and located bilaterally on the cerebellar cortex.

Striatal-to-cerebellum ratio (SCR) values of radioactivity counts were calculated in the 80-90-min frame for each structure, using bilaterally averaged cerebellar ROI data as the denominator. For subregional analysis of their association with major motor symptoms in the PD subjects, SCR values from the caudate nucleus and each part of the putamen were analyzed on the contralateral to the more affected side of limb.

### Statistical Analysis

For comparison of more than two groups, one-way analysis of variance (ANOVA) was used. When the one-way ANOVA was significant at $p < 0.05$, post-hoc comparisons were conducted using Scheffé's test. We examined the correlation of FMT uptake in each part of the putamen with disease duration, and with the symptoms of bradykinesia, tremor, rigidity, and postural instability assessed on UPDRS motor scores. Non-linear exponential regression analysis was applied to assess the relationship between FMT uptake and disease duration (Prism, GraphPad Software, La Jolla, CA). SCR values and the UPDRS scores were compared by Spearman's rank correlation coefficient test. $P < 0.05$ was considered to indicate a statistically significant difference.

## Results

### Characteristics of subjects

Demographic and clinical characteristics of the patients with PD and those of the control subjects are listed in Table 1 and Table 2. The mean ages of the PD patients (41 male and 60 female) and the control subjects (6 male and 13 female) were 64.0 years (SD 9.3) and 56.7

**Table 1 Clinical Characteristics of the Subjects**

| Characteristics | PD | Normal Control | *p* value |
|---|---|---|---|
| Age, year, mean ± SD | 64.0 ± 9.3 | 56.7 ± 11.1 | 0.005 |
| Male/Female | 41/60 | 6/13 | 0.542 |
| MMSE | 27 ± 2.6 | 29 ± 1.3 | 0.005 |

MMSE, Mini Mental State Examination.
Data are given as mean ± standard deviation (SD) values.

**Table 2 Clinical Charasteristics of the PD patients**

| | |
|---|---|
| Symptom duration, year | 6.0 ± 4.4 |
| More affected side | Right 55/Left 46 |
| Hoehn-Yahr stage, on | 2.4 ± 0.9 |
| Hoehn-Yahr stage, off | 3.3 ± 1.1 |
| UPDRS score | |
| Total motor | 30.3 ± 16 |
| Bradykinesia | 9.86 ± 6.3 |
| Rigidity | 6.15 ± 3.8 |
| Axial | 9.54 ± 6.2 |
| Tremor | 4.80 ± 4.0 |

UPDRS, Unified Parkinson's Disease Rating Scale.
Data are given as mean ± standard deviation (SD) values.

years (SD 11.1), respectively. A wide range of duration and severity of symptoms was represented among the patients. The mean duration of symptoms was 6.0 years (SD 4.4) and the mean UPDRS motor score was 30.3 (SD 16.0). The right side was more affected in 55 patients.

### Subregional analysis of FMT uptake

Figure 1 shows representative images of FMT uptake in a normal subject and in early- and late-stage PD patients. Among the patients, FMT uptake showed the most marked decrease in the posterior putamen, regardless of disease duration, but significant decrease was seen throughout the striatum compared with the healthy controls. There were significant differences between side (ipsi- vs. contralateral to the more affected limbs), region (anterior vs. posterior putamen), and diagnosis (healthy subjects vs. PD group) ($P < 0.001$) (Figure 2a). Asymmetry between the striatum of the more and less affected sides is preserved, but shows a decrease with disease progression (Figure 2b).

### Decline in FMT uptake with disease duration

Figure 3 shows scatterplots of FMT uptake against symptom duration in three regions of the putamen contralateral to the more affected limbs. Because age-related factors such as age at onset of symptoms and age-related Alzheimer-type pathology may influence disease duration, we excluded elderly-onset patients (> 70 years old; $n = 19$) in this analysis. Exponential regression curves that best fitted the data for each of the three regions analyzed are superimposed on the figure. Between 10 and 15 years of symptom duration, the FMT for all three curves leveled off to constant values that showed a statistically significant difference between the anterior and posterior putamen ($p < 0.001$). In the control group, there was no significant difference in SCR of FMT uptake between younger (< 59 years old, $n = 10$) and older (≥ 60 years old, $n = 9$) subjects (putamen, $p = 0.87$; caudate, $p = 0.81$).

### Correlation of cardinal symptoms and FMT uptake

To minimize the possibility of including patients with alternative diagnoses, we analyzed patients who had cardinal motor symptoms for at least 3 years ($n = 42$). We obtained positive correlations between the severities of major motor symptoms: rigidity vs. axial symptoms ($r = 0.68$, $p < 0.001$), rigidity vs. bradykinesia ($r = 0.56$, $p < 0.001$), bradykinesia vs. postural instability ($r = 0.54$, $p < 0.001$), and tremor vs. bradykinesia ($r = 0.39$, $p = 0.014$). However, tremor did not have a significant relation with rigidity ($r = 0.20$, $p = 0.20$) or with axial symptoms ($r =$

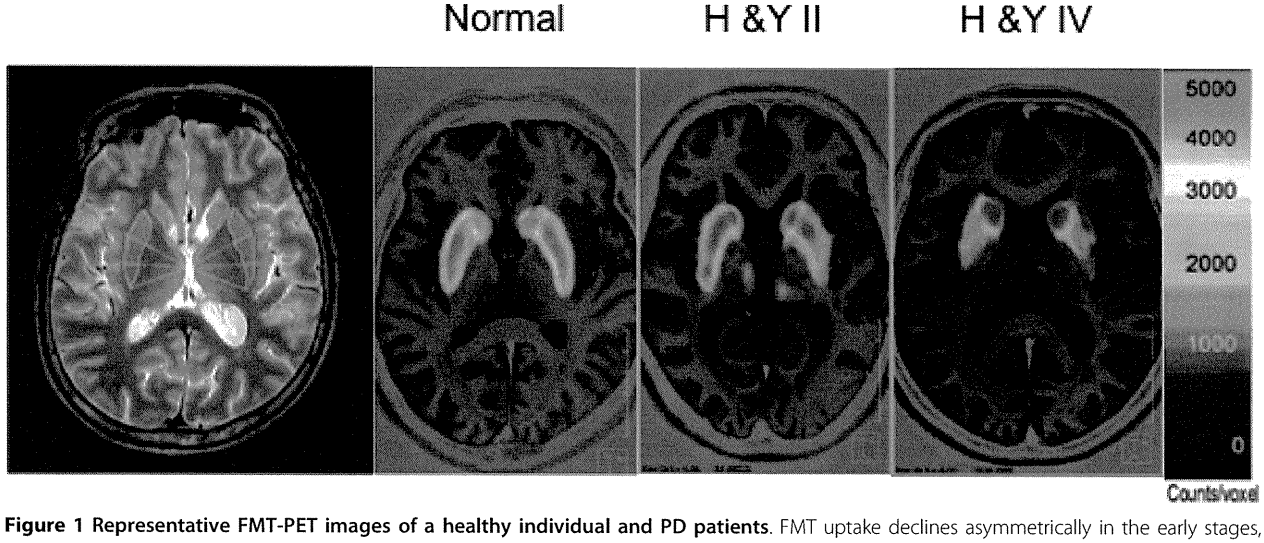


**Figure 1 Representative FMT-PET images of a healthy individual and PD patients.** FMT uptake declines asymmetrically in the early stages, mostly in the posterior putamen. Left: Regions-of-interest in the putamen. H &Y, Hohen and Yahr stage. The bar indicates the range of radioactive counts per voxel.

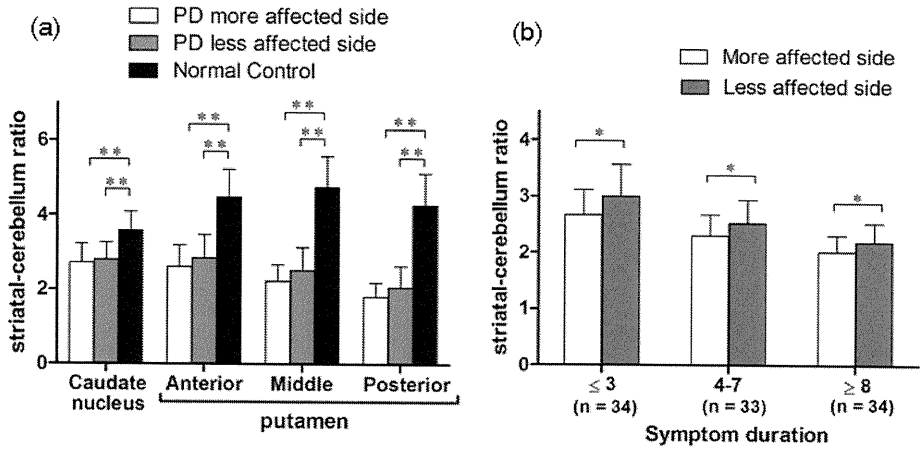


**Figure 2 FMT uptake in different subregions of the striatum**. Mean FMT uptake in different subregions of the striatum in normal control and PD patients (a). Comparison by side (b) shows persistant side-side asymmetry of putaminal uptake throughout the disease course. *$P < 0.05$, ** $P < 0.01$.

0.12, $p = 0.45$). Axial symptoms, rigidity, and bradykinesia scores showed a correlation with FMT uptake in the contralateral putamen, with the highest correlation in the anterior putamen, but not in the contralateral caudate (Table 3). No significant correlation was evident between unilateral tremor scores from the most severely affected limbs and any of the striatal regions. To assess the potential influence of age, we analyzed older patients (> 60 years old; $n = 25$) separately and found similar correlations between major symptoms and FMT uptake (Table 4).

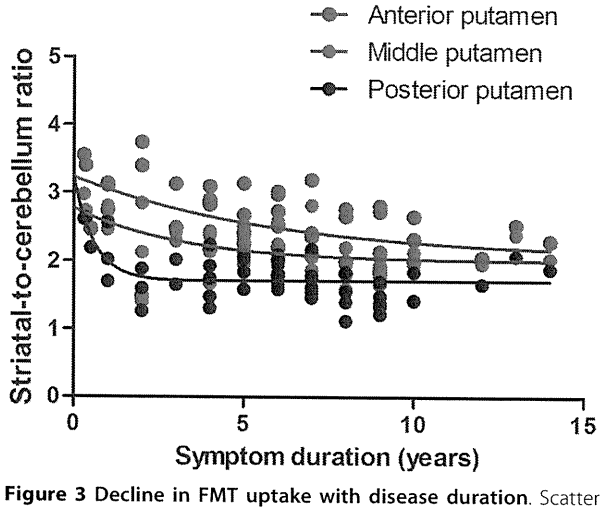


**Figure 3 Decline in FMT uptake with disease duration**. Scatter plots of FMT uptake against symptom duration in the putamen contralateral to the more affected limb in PD patients. Exponential decline is observed in all subregions of the putamen. Reduction of uptake is prominent at onset of the disease.

## Discussion

Idiopathic PD is defined as a synucleinopathy in which Lewy bodies, pathological aggregations of the synaptic protein α-synuclein, are found in the dopaminergic neurons in the substantia nigra [14,15]. A reduction of dopamine in the striatum is a consistent finding in PD, although the clinical features are heterogeneous and include different predominant symptoms (resting tremor, bradykinesia, rigidity, or postural instability and gait disorder) with different rates of progression, and with or without dementia [16-19]. PET imaging is a valuable tool for assessing altered dopaminergic function in the striatum in PD. While FDOPA is suitable for assessing the metabolism of levodopa, FMT is superior for estimating AADC activity because it enables the production of higher-quality brain images [7,20-22]. The high resolution of FMT-PET images enables analysis of

**Table 3 Correlations of UPDRS scores and FMT uptake ratio values in the each part of the putamen**

| Putamen | Anterior | Middle | Posterior | Whole |
|---|---|---|---|---|
| Symptom duration, year | -0.52 (<0.001) | -0.56 (<0.001) | -0.51 (<0.001) | -0.58 (<0.001) |
| Total motor score | -0.56 (<0.001) | -0.48 (0.002) | -0.41 (0.008) | -0.51 (0.001) |
| Bradykinesia | -0.54 (<0.001) | -0.53 (<0.001) | -0.44 (0.005) | -0.55 (<0.001) |
| Rigidity | -0.50 (0.001) | -0.43 (0.006) | -0.37 (0.018) | -0.44 (0.005) |
| Axial | -0.60 (<0.001) | -0.51 (0.001) | -0.37 (0.016) | -0.50 (0.001) |
| Tremor | 0.069 (0.658) | 0.085 (0.587) | 0.015 (0.925) | 0.050 (0.747) |

Data are given as $r$ ($p$) values. These values were calculated by Spearman's rank correlation coefficient test. UPDRS motor score in off-medication state was evaluated in 42 subjects.

**Table 4 Correlations of UPDRS scores and FMT uptake ratio values in the each part of the putamen in elder patients**

| Putamen | Anterior | Middle | Posterior | Whole |
|---|---|---|---|---|
| Symptom duration, year | -0.70 (<0.001) | -0.63 (<0.005) | -0.45 (<0.05) | -0.70 (<0.001) |
| Total motor score | -0.56 (<0.01) | -0.50 (<0.05) | -0.37 (0.07) | -0.49 (<0.05) |
| Bradykinesia | -0.46 (<0.05) | -0.46 (<0.05) | -0.34(0.08) | -0.46 (<0.05) |
| Rigidity | -0.46 (<0.05) | -0.39 (0.05) | -0.31 (0.12) | -0.37 (0.06) |
| Axial | -0.69 (<0.001) | -0.59 (<0.01) | -0.45 (<0.05) | -0.58 (<0.01) |
| Tremor | 0.26 (0.21) | 0.12 (0.58) | 0.06 (0.77) | 0.14 (0.51) |

Data are given as *r* (*p*) values. These values were calculated by Spearman's rank correlation coefficient test. UPDRS motor score in off-medication state was evaluated in 25 subjects.

dopaminergic presynaptic changes in each subregion of the striatum.

In the present study, FMT uptake in PD was reduced in the putamen, particularly in the posterior part. The anterior-to-posterior gradient of the uptake decrease in the putamen persisted to the advanced stage of PD. These results are consistent with those of previous reports that used other tracers of presynaptic dopaminergic terminals, and are considered to reflect the selective degeneration of nigrostriatal pathways that project into the posterior part of the putamen [23-25]. The lowest value of FMT uptake was observed in the posterior part of the putamen contralateral to the more affected limbs, even in the early stage of the disease. Because we analyzed regions in the posterior one-third of the putamen on high-resolution images, it is unlikely that the decreases in uptake were caused by partial volume effects, which may arise from placement of a small ROI on inaccurately co-registered images.

Post-mortem investigations of PD demonstrate that the rate of decrease of nigral neurons is rapid in the initial stage of the disease: approximately 40%-50% are lost in the first decade, possibly with a slower rate of degeneration later on, to finally approach a normal age-related linear decline [26]. In the present study, loss of FMT was well fitted to symptom duration using a single exponential approximation. The exponential model provided a better fit than a linear model, indicating that the rate of decline in FMT uptake in the contralateral putamen was faster at the beginning of the disease and slowed down as the disease progressed, in agreement with the results of previous studies that used radiotracers for imaging nigrostriatal nerve terminals [23-25]. Because we performed cross-sectional analysis in the present study, and because all of the participants were on medication, the data do not provide accurate information regarding the natural course of the disease, even if PET measurements were taken in off-medication state. Even so, the present data are important for assessing the progression of dopaminergic hypofunction in the striatum under optimal medical treatment, and can provide the basis for the development of even better therapeutic strategies [27,28].

We applied striatal count ratios to analyze the relationships between subregional putaminal FMT uptake and clinical symptoms. Striatal count ratios using the cerebellum as the denominator have a strong correlation with striatal uptake constants (Ki values) [29,30]. The present FMT-PET study showed a significant correlation between cardinal motor symptoms (rigidity, bradykinesia, and axial symptoms) and uptake of the tracer in the putamen, and no significant correlation was found between tremor score and FMT uptake. These findings are consistent with the results of previous PET studies [31-33]. The clinical correlations were more significant in the anterior part of the putamen than in the posterior part, possibly reflecting a floor effect for the uptake of FMT in the posterior part of the putamen, where the decrease was severe even in the early stage of the disease.

The pathophysiological mechanism of tremor is not fully understood [34]. Tremor does not respond to L-dopa as well as do bradykinesia and rigidity. The fact that stereotactic lesion or deep brain stimulation of the ventral intermediate nucleus (Vim) of the thalamus successfully improves tremor indicates a strong association between non-dopaminergic thalamic and cerebellar systems, and tremor generation [35,36].

## Conclusions

Our results indicate that FMT-PET is useful for evaluating PD patients from the early stage of the disease and for studying the relationship between AADC activity and various clinical features. Decrease of FMT uptake in the posterior putamen appears to be most sensitive in mild PD, and uptake in the anterior putamen may reflect the severity of main motor symptoms, except for tremor. These data provide an important baseline for evaluating the effects of surgical interventions, such as gene therapy for PD.

**Acknowledgements**

This study was supported by grants from the Japanese Government: a Grant-in-Aid from the Research Committee of CNS Degenerative Diseases via the Ministry of Health, Labour and Welfare, and grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan. The authors would like to thank Jun-ichi Saito and Seiji Nagashima for their technical assistance.

**Author details**

[1]Division of Neurology, Department of Medicine, Jichi Medical University, Tochigi, Japan. [2]WebNet Technology, Tochigi, Japan. [3]Utsunomiya Central Clinic, Tochigi, Japan.

**Authors' contributions**

SA participated in designing the study, data collection, conducted the statistical analyses, interpreted data and drafted the first manuscript.
KF participated in data collection and interpretation of data.
AM participated in data collection and interpretation of data.
TS participated in data collection and interpretation of data.
IN participated in designing the study and interpretation of data.
SM conceived the study, participated in its design, data collection, interpretation of data and drafting the manuscript.
All authors read and approved the final manuscript.

**Competing interests**

The authors declare that they have no competing interests.

Received: 6 October 2010 Accepted: 23 March 2011
Published: 23 March 2011

**References**

1. Hornykiewicz O: **Biochemical aspects of Parkinson's disease.** *Neurology* 1998, **51**:S2-9.
2. Nagatsu T, Ichinose H: **Molecular biology of catecholamine-related enzymes in relation to Parkinson's disease.** *Cell Mol Neurobiol* 1999, **19**:57-66.
3. Halliday G: **Substantia nigra and locus coeruleus.** In *The human nervous system.* 2 edition. Edited by: Paxinos G, Mai JK. Amsterdam; Boston: Elsevier Academic Press; 2004:pp457-458.
4. Garnett ES, Firnau G, Nahmias C: **Dopamine visualized in the basal ganglia of living man.** *Nature* 1983, **305**:137-138.
5. Pate BD, Kawamata T, Yamada T, McGeer EG, Hewitt KA, Snow BJ, Ruth TJ, Calne DB: **Correlation of striatal fluorodopa uptake in the MPTP monkey with dopaminergic indices.** *Ann Neurol* 1993, **34**:331-338.
6. Snow BJ, Tooyama I, McGeer EG, Yamada T, Calne DB, Takahashi H, Kimura H: **Human positron emission tomographic [$^{18}$F]fluorodopa studies correlate with dopamine cell counts and levels.** *Ann Neurol* 1993, **34**:324-330.
7. DeJesus OT, Flores LG, Murali D, Converse AK, Bartlett RM, Barnhart TE, Oakes TR, Nickles RJ: **Aromatic l-amino acid decarboxylase turnover in vivo in rhesus macaque striatum: a microPET study.** *Brain Res* 2005, **1054**:55-60.
8. DeJesus OT, Holden JE, Endres C, Murali D, Oakes TR, Shelton S, Uno H, Houser D, Freund L, Perlman SB, *et al*: **Visualization of dopamine nerve terminals by positron tomography using [$^{18}$F]fluoro-β-fluoromethylene-*m*-tyrosine.** *Brain Res* 1992, **597**:151-154.
9. Doudet DJ, Chan GL, Jivan S, DeJesus OT, McGeer EG, English C, Ruth TJ, Holden JE: **Evaluation of dopaminergic presynaptic integrity: 6-[$^{18}$F] fluoro-l-dopa versus 6-[$^{18}$F]fluoro-l-*m*-tyrosine.** *J Cereb Blood Flow Metab* 1999, **19**:278-287.
10. Eberling JL, Bankiewicz KS, O'Neil JP, Jagust WJ: **PET 6-[$^{18}$F]fluoro-l-*m*-tyrosine Studies of Dopaminergic Function in Human and Nonhuman Primates.** *Front Hum Neurosci* 2007, **1**:9.
11. Hughes AJ, Daniel SE, Lees AJ: **Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease.** *Neurology* 2001, **57**:1497-1499.
12. Maes F, Collignon A, Vandermeulen D, Marchal G, Suetens P: **Multimodality image registration by maximization of mutual information.** *IEEE Trans Med Imaging* 1997, **16**:187-198.
13. Wells WM, Grimson WL, Kikinis R, Jolesz FA: **Adaptive segmentation of MRI data.** *IEEE Trans Med Imaging* 1996, **15**:429-442.
14. Dickson DW, Braak H, Duda JE, Duyckaerts C, Gasser T, Halliday GM, Hardy J, Leverenz JB, Del Tredici K, Wszolek ZK, Litvan I: **Neuropathological assessment of Parkinson's disease: refining the diagnostic criteria.** *Lancet Neurol* 2009, **8**:1150-1157.
15. Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M: **Alpha-synuclein in Lewy bodies.** *Nature* 1997, **388**:839-840.
16. Halliday GM, McCann H: **The progression of pathology in Parkinson's disease.** *Ann N Y Acad Sci* 2010, **1184**:188-195.
17. Maetzler W, Liepelt I, Berg D: **Progression of Parkinson's disease in the clinical phase: potential markers.** *Lancet Neurol* 2009, **8**:1158-1171.
18. Selikhova M, Williams DR, Kempster PA, Holton JL, Revesz T, Lees AJ: **A clinico-pathological study of subtypes in Parkinson's disease.** *Brain* 2009, **132**:2947-2957.
19. van Rooden SM, Heiser WJ, Kok JN, Verbaan D, van Hilten JJ, Marinus J: **The identification of Parkinson's disease subtypes using cluster analysis: a systematic review.** *Mov Disord* 2010, **25**:969-978.
20. Brown WD, DeJesus OT, Pyzalski RW, Malischke L, Roberts AD, Shelton SE, Uno H, Houser WD, Nickles RJ, Holden JE: **Localization of trapping of 6-[$^{18}$F]fluoro-l-*m*-tyrosine, an aromatic l-amino acid decarboxylase tracer for PET.** *Synapse* 1999, **34**:111-123.
21. DeJesus OT, Haaparanta M, Solin O, Nickles RJ: **6-fluoroDOPA metabolism in rat striatum: time course of extracellular metabolites.** *Brain Res* 2000, **877**:31-36.
22. Elsinga PH, Hatano K, Ishiwata K: **PET tracers for imaging of the dopaminergic system.** *Curr Med Chem* 2006, **13**:2139-2153.
23. Bruck A, Aalto S, Rauhala E, Bergman J, Marttila R, Rinne JO: **A follow-up study on 6-[$^{18}$F]fluoro-l-dopa uptake in early Parkinson's disease shows nonlinear progression in the putamen.** *Mov Disord* 2009, **24**:1009-1015.
24. Lee CS, Schulzer M, de la Fuente-Fernandez R, Mak E, Kuramoto L, Sossi V, Ruth TJ, Calne DB, Stoessl AJ: **Lack of regional selectivity during the progression of Parkinson disease: implications for pathogenesis.** *Arch Neurol* 2004, **61**:1920-1925.
25. Nandhagopal R, Kuramoto L, Schulzer M, Mak E, Cragg J, Lee CS, McKenzie J, McCormick S, Samii A, Troiano A, *et al*: **Longitudinal progression of sporadic Parkinson's disease: a multi-tracer positron emission tomography study.** *Brain* 2009, **132**:2970-2979.
26. Fearnley JM, Lees AJ: **Ageing and Parkinson's disease: substantia nigra regional selectivity.** *Brain* 1991, **114(Pt 5)**:2283-2301.
27. Christine CW, Starr PA, Larson PS, Eberling JL, Jagust WJ, Hawkins RA, VanBrocklin HF, Wright JF, Bankiewicz KS, Aminoff MJ: **Safety and tolerability of putaminal AADC gene therapy for Parkinson disease.** *Neurology* 2009, **73**:1662-1669.
28. Muramatsu SI, Fujimoto KI, Kato S, Mizukami H, Asari S, Ikeguchi K, Kawakami T, Urabe M, Kume A, Sato T, *et al*: **A Phase I study of aromatic l-amino acid decarboxylase gene therapy for Parkinson's disease.** *Mol Ther* 2010, **18**:1731-1735.
29. Dhawan V, Ma Y, Pillai V, Spetsieris P, Chaly T, Belakhlef A, Margouleff C, Eidelberg D: **Comparative analysis of striatal FDOPA uptake in Parkinson's disease: ratio method versus graphical approach.** *J Nucl Med* 2002, **43**:1324-1330.
30. Eberling JL, Pivirotto P, Bringas J, Bankiewicz KS: **Comparison of two methods for the analysis of [$^{18}$F]6-fluoro-l-*m*-tyrosine PET data.** *Neuroimage* 2004, **23**:358-363.
31. Martin WR, Wieler M, Stoessl AJ, Schulzer M: **Dihydrotetrabenazine positron emission tomography imaging in early, untreated Parkinson's disease.** *Ann Neurol* 2008, **63**:388-394.
32. Otsuka M, Ichiya Y, Kuwabara Y, Hosokawa S, Sasaki M, Yoshida T, Fukumura T, Masuda K, Kato M: **Differences in the reduced $^{18}$F-Dopa uptakes of the caudate and the putamen in Parkinson's disease: correlations with the three main symptoms.** *J Neurol Sci* 1996, **136**:169-173.
33. Vingerhoets FJ, Schulzer M, Calne DB, Snow BJ: **Which clinical sign of Parkinson's disease best reflects the nigrostriatal lesion?** *Ann Neurol* 1997, **41**:58-64.
34. Rodriguez-Oroz MC, Jahanshahi M, Krack P, Litvan I, Macias R, Bezard E, Obeso JA: **Initial clinical manifestations of Parkinson's disease: features and pathophysiological mechanisms.** *Lancet Neurol* 2009, **8**:1128-1139.
35. Diamond A, Shahed J, Jankovic J: **The effects of subthalamic nucleus deep brain stimulation on parkinsonian tremor.** *J Neurol Sci* 2007, **260**:199-203.
36. Terao T, Yokochi F, Taniguchi M, Kawasaki T, Okiyama R, Hamada I, Nishikawa N, Izawa N, Shin M, Kumada S, Takahashi H: **Microelectrode findings and topographic reorganisation of kinaesthetic cells after gamma knife thalamotomy.** *Acta Neurochir (Wien)* 2008, **150**:823-827, discussion 827.

**Pre-publication history**

The pre-publication history for this paper can be accessed here:
http://www.biomedcentral.com/1471-2377/11/35/prepub

doi:10.1186/1471-2377-11-35
**Cite this article as:** Asari *et al.*: Subregional 6-[$^{18}$F]fluoro-L-*m*-tyrosine Uptake in the Striatum in Parkinson's Disease. *BMC Neurology* 2011 11:35.