Clinical features of familial Parkinson’s disease in Thai patients

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ABSTRACT

Background Parkinson’s disease (PD) is the second most common neurodegenerative disease. Most cases are sporadic, but family history is also observed in certain cases.

This study aimed to describe the clinical features of familial PD in Thai patients.

Method The study included five female and three male patients from a Malay family of consanguineous parents who were evaluated for clinical study. Every patient was examined initially at the outpatient unit of the family medicine department. The diagnosis was later confirmed by a team of neurologists at the division of neurology, department of medicine. The patients were first seen and evaluated in 1999, with subsequent evaluation in 2005 and 2008.

Results Clinical features such as tremor, rigidity, bradykinesia and postural instability were similar to those of the classical idiopathic PD, but age of onset was earlier. The interval between the onset of parkinsonism and first presentation was 1–3 years, and PD was diagnosed within 1–4 years of the onset of parkinsonism. The median age at disease onset was 31 years (range 27 to 49 years). The severity of clinical symptoms and signs was different among affected family members, from stage I to IV of the Hoehn and Yahr stage scale. Motor dysfunction and other complications were observed. The family history suggested that the condition was being passed on only from the maternal side.

Conclusions The clinical features of familial PD are generally indistinguishable from classical PD, although the diagnosis may be difficult in atypical presentations such as palpitation, anxiety and insomnia. The disease tends to develop earlier in younger siblings. Family members were at greater risk of autosomal recessive disorders that are homozygous for a particular recessive gene mutation due to consanguineous parents. On the other hand, specific ethnicity, very early onset of symptoms, rapid progression of the disease, and high family incidence suggested autosomal dominant inheritance. Since each family member displayed different symptoms and signs, this may have indicated variable penetrance of the PD gene, but the results are not conclusive due to lack of medical records from other relatives and genetic studies.

Keywords: clinical features, family pedigree, genogram, Parkinson’s disease, Thailand
Introduction

Parkinson’s disease (PD) is the second most common neurodegenerative disease. It is characterised by degeneration of dopaminergic neurones in the substantia nigra pars compacta, and the presence of Lewy bodies of the midbrain.\(^1\) The onset is usually in the late 50s,\(^2\)\(^–\)\(^4\) and it appears less frequently in the young.\(^2\)\(^,\)\(^3\) The disease becomes progressive with time, which contributes to shortened life expectancy.\(^2\)\(^,\)\(^3\) The majority of patients (70–98%) are sporadic, while 10–30% are familial.\(^5\) Complex gene–gene and gene–environmental interactions contribute to the pathogenesis of PD.\(^1\)\(^,\)\(^6\) Certain environmental factors such as methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a meperidine derivative, and rotenone, commonly used insecticides, may cause nigrostriatal damage.\(^1\)\(^,\)\(^6\) Although genetic transmission is well documented, both autosomal dominant,\(^3\)\(^,\)\(^7\)\(^–\)\(^12\) and recessive modes of inheritance,\(^1\)\(^,\)\(^13\)\(^,\)\(^14\) family pedigrees that reveal clear Mendelian inheritance, are uncommon.\(^4\)\(^,\)\(^15\) Recently, genes have been identified for familial and young-onset sporadic PD. The examples of autosomal dominant genes identified are \(\alpha\)-synuclein (\(SNCA\)) and leucine rich repeat kinase 2 (\(LRRK2\)).\(^1\) Autosomal recessive genes such as parkin (\(PARK2\)), \(PINK1\) and \(DJ\)-\(1\), have also been discovered.\(^3\) Nonetheless, the cost of genetic studies is high, and in developing countries where funds are scarce and most patients have low incomes, these expensive tests may not be appropriate for traditional primary health care. As a conscious choice, most primary care physicians have to rely solely on clinical signs and symptoms as well as the patient’s family history to diagnose familial PD and/or young-onset sporadic PD. Before the emergence of genetic studies, the family tree diagram was widely used in academic settings and medical practice to establish patterns of inheritance within families, and it still plays an important role in modern-day primary health care. With this inexpensive technique, familial PD can still be diagnosed as well as helping to determine its apparent mode of inheritance.

PD is a common medical problem in Thailand. It ranked as the fifth most common disorder seen by neurologists.\(^1\)\(^6\) However, familial PD has never been reported. A family of eight siblings was investigated in this study due to the high incidence of PD in the family and early onset of symptoms. A family tree diagram was constructed to ascertain familial PD and the possible mode of inheritance.

The objective of this study was to describe the clinical features of familial Parkinson’s disease in Thai patients.

Method

The study focused on a family with eight siblings. All of whom had the same parents. Their parents were consanguineous, being first cousins. Every patient was examined initially at the outpatient unit of the family medicine department. The diagnosis was later confirmed by a team of neurologists at the division of neurology, department of medicine. The patients were first seen and evaluated in 1999, with subsequent evaluations in 2005 and 2008. The study was approved by the Committee on Human Rights Related to Researches Involving Human Subjects, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand.

Results

Clinical manifestations

The family included eight siblings, three males and five females. Five siblings developed clinical signs and symptoms of PD. The other two siblings had no clinical symptoms but displayed neurological signs upon examination. Five of the seven patients (two males and three females) developed their first symptoms at ages 49, 31, 38, 31, and 28 years (cases IV-1, IV-2, IV-4, IV-6 and IV-7 respectively). They were diagnosed within 1 to 4 years after the onset of parkinsonian symptoms and signs. Two subjects (cases IV-5, and IV-8) were diagnosed at the time of
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initial neurological examinations, without exhibiting any clinical symptoms. They were 38 and 27 years old respectively (see Table 1). Only case IV-2 was diagnosed with PD prior to this study (in 1985).

Case series

Case IV-4 was the originating case at Ramathibodi Hospital, leading to the subsequent diagnosis of familial PD. The other seven siblings (cases IV-1, IV-2, IV-3, IV-5, IV-6, IV-7 and IV-8) were invited for further clinical evaluation. Only six of the seven invited patients were affected. These six patients received medical intervention at different healthcare facilities. The case series are presented according to the age of the patients.

Case IV-1: first sibling – 50-year-old female

This 50-year-old female initially presented with declining dexterity while doing embroidery in 1999. She had noticed that her hands moved more slowly and needed more time to complete the work. She stated that her symptoms had developed one year prior to this. During the interview, she admitted to having the symptoms of fatigue and exertional dyspnoea.

On neurological examination, rest tremor was not found. Her arm swing was decreased on the left side, with cogwheel rigidity during a reinforcement manoeuvre (i.e. with the contralateral arm moved up and down). Postural stability and gait were normal. Her cognitive status was normal. The diagnosis of PD was made in 1999. No medication was prescribed. Subsequent follow-up in the year 2005 and 2008 showed no progression of symptoms, and no medication was given.

Case IV-2: second sibling – 47-year-old male

The patient was 31 years old (in 1983), when he started to have numbness of the left-sided extremities with generalised fatigue and weakness. Within the next two years he developed tremor, anxiety and insomnia. The tremor worsened when he was scared or excited. These symptoms caused him to seek medical care. In 1985, he was diagnosed with PD. Levodopa/benserazide (100/25 mg) was prescribed twice daily.

In 1999, resting tremor, cogwheel rigidity and left-sided dyskinesia were noticed. Mental function was normal. He received levodopa/benserazide. In 2005, Hoehn and Yahr stage 3 was reduced to stage 1 while on levodopa. Dyskinesia, abnormal posture, bradykinesia, rigidity, and tremor were more marked. The neurological signs were more marked on the left side compared with the right. Ability to draw and write were affected. The frequency of levodopa was increased to

<table>
<thead>
<tr>
<th>Case number</th>
<th>Age (years) (1999)</th>
<th>Sex</th>
<th>Time since symptom onset (years)</th>
<th>Age at symptom onset (years)</th>
<th>H&amp;Y stage</th>
</tr>
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<tr>
<td>IV-1</td>
<td>50</td>
<td>F</td>
<td>1</td>
<td>49</td>
<td>2</td>
</tr>
<tr>
<td>IV-2</td>
<td>47</td>
<td>M</td>
<td>2</td>
<td>31</td>
<td>3</td>
</tr>
<tr>
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<td>38</td>
<td>3</td>
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<tr>
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<td>F</td>
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<td>38</td>
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</tr>
<tr>
<td>IV-5</td>
<td>38</td>
<td>F</td>
<td>–</td>
<td>38</td>
<td>1</td>
</tr>
<tr>
<td>IV-6</td>
<td>34</td>
<td>M</td>
<td>3</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>IV-7</td>
<td>31</td>
<td>F</td>
<td>3</td>
<td>28</td>
<td>3</td>
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<tr>
<td>IV-8</td>
<td>27</td>
<td>M</td>
<td>–</td>
<td>27</td>
<td>1</td>
</tr>
</tbody>
</table>

*a H&Y, Hoehn and Yahr stage: stage 0, no signs of disease; stage 1, unilateral disease; stage 1.5, unilateral plus axial involvement; stage 2, bilateral disease without impairment of balance; stage 2.5, mild bilateral disease with recovery on full rest; stage 3, mild to moderate bilateral disease, some postural instability, physically independent; stage 4, severe disability, still able to walk or stand unassisted; stage 5, wheelchair-bound or bedridden unless aided.

Figure 1 Familial pedigree of familial Parkinson’s disease
every three hours on the same dosage. In 2007, the
dosage was increased to every two hours. At sub-
sequent follow-up in 2008, abnormal jerking of the
extremities was observed for 30 minutes after taking
levodopa. For the previous 7 months he had been
experiencing falls while walking (see Table 2). He
continued to take levodopa every 2 hours.

**Case IV-3: third sibling – 43-year-old female, normal case**

This 43-year-old female had no clinical signs or
symptoms of PD.

**Case IV-4: fourth sibling – 42-year-old female, index case**

The patient started to have palpitations and experi-
enced tremor affecting her right hand when she was 38
years old. She was having occasional insomnia. These
symptoms were mild but she sought medical atten-
tion. Her symptoms had increased progressively for
15 months before the diagnosis. She was suffering
from anxiety, and increasing palpitations. Thyroid
function was normal. During this time, she visited
Ramathibodi hospital on seven occasions. After a further
family history was obtained (a brother, case IV-2, with
similar symptoms was diagnosed with PD earlier) and
successive neurological evaluations were performed,
familial PD was diagnosed in February 1999. Neuro-
logical evaluation in 1999 exhibited rest tremor in
both hands, although it was more marked on the right.
Exhaustion, rigidity, slowness of movement and dys-
phonia were more pronounced in the evening. She was
unsteady while walking and turning. She also occa-
sionally felt a sudden falling backward upon rising to
an erect position, necessitating a few steps backwards
to retain an upright posture and a balance. Her fear of
having PD like her mother (case III-3) and her siblings
(cases IV-2 and IV-7) had become more prominent as
the symptoms got worse. Nevertheless, she could still
perform daily activities after taking levodopa/carbidopa
(100/25 mg) half a tablet twice daily.

<table>
<thead>
<tr>
<th>Initial symptoms</th>
<th>Generation-case</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>IV-1</td>
</tr>
<tr>
<td>Tremor</td>
<td>0</td>
</tr>
<tr>
<td>Rigidty</td>
<td>+</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>+</td>
</tr>
<tr>
<td>Postural</td>
<td>0</td>
</tr>
<tr>
<td>instability</td>
<td></td>
</tr>
<tr>
<td>Gait difficulty</td>
<td>0</td>
</tr>
<tr>
<td>Speech problems</td>
<td>0</td>
</tr>
<tr>
<td>Motor</td>
<td></td>
</tr>
<tr>
<td>complications</td>
<td></td>
</tr>
<tr>
<td>l-dopa-induced</td>
<td>0</td>
</tr>
<tr>
<td>dyskinesia</td>
<td></td>
</tr>
<tr>
<td>Wearing off</td>
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</tr>
<tr>
<td>On–off phenomena</td>
<td>0</td>
</tr>
<tr>
<td>Freezing</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>complications</td>
<td></td>
</tr>
<tr>
<td>Sialorrhoea</td>
<td>0</td>
</tr>
<tr>
<td>Falls</td>
<td>0</td>
</tr>
</tbody>
</table>

N = normal, 0 = absent, + = present
In 2005, her physical examination was the same as in 1999, except the Hoehn and Yahr stage was increased from stage 2 to stage 3. Her mental function was normal. She kept herself in good condition by jogging 30 minutes per day. From 1999 to 2007, there was a gradual increased in frequency of levodopa necessary to maintain her normal daily activities.

**Case IV-5: fifth sibling – 38-year-old female, asymptomatic case**

In 1999, she had no apparent symptoms but reduction of her left arm swing was detected. No medication was given. There was no progression of symptoms on follow-up.

**Case IV-6: sixth sibling – 34-year-old male**

Three years prior to presentation, the patient’s symptoms began with resting tremor of his left hand and hyperextension of the fingers. One month before the diagnosis, he felt unsteady. In 1999, cogwheel rigidity was detected. By 2005, resting tremor, bradykinesia and absent arm swing on the left were also evident. The patient did not require any medication.

**Case IV-7: seventh sibling – 28-year-old female**

The patient developed stiffness and slowness of her left arm and fatigue three years before the diagnosis but did not seek medical attention. The reduced arm swing became bilateral four months before attending Ramathibodi hospital. At presentation in 1999, there was mild axial rigidity, cogwheel rigidity on both hands, a reduction of left arm swing, and hyperreflexia. Resting tremor was not detected. After taking levodopa/carbidopa (100/25 mg) half a tablet twice a day, she was able to perform normal activities. Resting tremor, cogwheel rigidity and bradykinesia were evident by 2005. Mental function was normal. Levodopa was increased in frequency to three times a day in 2005 and eventually to five times a day in 2007.

**Case IV-8: eighth sibling – 27-year-old male, asymptomatic case**

This patient had no symptoms apparent in 1999. Only reduction of left arm swing was detected. No medication was given. There was no progression of symptoms on follow-up.

**Case III-1: Male – dead**

This was one of the maternal uncles of the family under study. The other family members stated that he had developed similar symptoms and signs as his sister, case III-3. His family suspected that his symptoms started in his 50s. He did not seek medical attention. Further medical history was unknown.

**Case III-3: Female died aged 54 years old**

This patient’s history was obtained from her children, cases IV-1, IV-2 and IV-3. She had slowness of movements and reduction in right arm swing by the age of 31 years. She developed right hemiparesis at the age around 40 years, and became bedridden at the age of 44 years (1977). She received medical care at a different hospital. Her medical record could not be retrieved.

**Family pedigree (see Figure 1)**

All of the family members were of Thai-Malay ethnicity and came from the southern part of Thailand. There was a consanguineous marriage, between cases III-3 and III-6.

**Laboratory findings**

Complete blood count, serum chemistry, serum copper, serum ceruloplasmin and urinalysis were normal for all the patients. Mild thinning of the pars compacta in the midbrain was detected from magnetic resonance imaging/angiogram (MRI/MRA) of the brain for index case IV-4 on 24 May 2005.

Since there are other inherited syndrome associated with parkinsonism, three subjects (case IV-4, IV-6 and IV-7) were evaluated for Wilson’s disease as well. Plasma caeruloplasmin was normal and examination for Kayser–Fleischer (KF) rings, performed by an ophthalmologist was negative in each case.

**Discussion**

PD has distinctive clinical features, but the accuracy of diagnosis improves with time and repeated assessment. The diagnosis may be supported by traditional imaging (to exclude secondary causes) and by functional imaging studies (e.g. fluorodopa positron emission topography). The accuracy of clinical diagnosis can be high in expert hands, estimated at 82%, by applying Parkinson’s Disease Society Brain Bank (PDSBB) clinical diagnostic criteria. PD can be misdiagnosed due to unusual presentation such as early onset, early stage of disease or atypical symptoms.

The median age at onset in this family was 31 years (mean age was 34.6 ± 7.7 years), which is earlier than the usual age of onset (46.5–67 years) previously reported. Male family members started their symptoms (at 31, 31 and 27 years old) earlier than female patients (aged 49, 38, 38 and 28 years old). The interval between the onset of parkinsonism and the first medical examination was 1–3 years, which was shorter compared to the previously reported 3.5–6
years by Hoehn and Yahr. Socio-economic factors played a role in patients’ decisions to seek medical care.

The diagnosis of PD could have been overlooked in this family since they presented at a very young age. Some family members (cases IV-5 and IV-8) did not exhibit any symptoms. Because of the family history, the diagnosis of PD was expedited for other family members. This study illustrates the practical value of family history and the family genogram, which allowed us to recognize familial PD clinically.

The mode of PD transmission in this family could have been either autosomal recessive or autosomal dominant. The family pedigree showed that seven of eight siblings were affected at an early age. More importantly, they were from a consanguineous marriage. The offspring of consanguineous relationships are at greater risk of autosomal recessive disorders. These occur in individuals who are homozygous for a recessive gene mutation. The family history revealed that the affected individuals were on the maternal side (the mother and one of the maternal uncles). If both had PD, they were each likely to have been homozygous for an autosomal recessive PD gene. Since this family had such a high prevalence of PD in generation IV, at least one of the parents should have been homozygous for a recessive PD gene, with the other parent having a heterozygous recessive gene. This particular assumption produces a 50% chance of having children with PD. Mutations in the parkin gene (PARK2) and PINK1 gene are common cause of early-onset PD and autosomal recessive PD worldwide. Furthermore, mutations in the DJ-1 gene are also associated with early-onset PD and autosomal recessive PD, particularly in European and Asian populations.

In autosomal dominant diseases, most of the cases are heterozygous for the defective gene, while homozygous cases are rarely observed. In families where both parents are affected, the probands are homozygous for the defective PD gene, which might lead to a more aggressive pathological process and earlier onset of symptoms than in heterozygous relatives. The disease onset at earlier age in subsequent generations (termed ‘anticipation’) has been reported in unilateral transmitted cases with only one parent affected as well. This family had a history of suspected PD in the maternal side and could represent an example of ‘anticipation’.

Mutation in the α-synuclein (SNCA) gene, 4q21 can cause an autosomal dominant inheritance transmission for PD, which is more common in families from Greece, Southern Italy and Germany. A recently discovered mutation is LRRK2 (PARK8; 12p11-q13), the most frequent known cause of autosomal dominant familial PD. However, it also found in some sporadic cases of familial PD due to incomplete penetrance. Moreover, there are many mutations in the LRRK2 gene. A common LRRK2 (G2019S) variant has been identified among people from Europe, North Africa, and Ashkenazi Jews, while an LRRK2 variant, Gly2385Arg has been demonstrated in Japanese, Chinese populations from Taiwan, Singapore, and mainland China, and non-Chinese Asians of Malay ethnicity, which suggests the possibility of specific genetic mutations in certain ethnic groups. Due to variability in clinical presentation among family members, we suspect the causative autosomal dominant gene in this case might also have high variable penetrance. Nevertheless, genetic testing is important for identifying specific genetic mutation in this family.

Finally, there are several inherited syndromes associated with parkinsonism, including Wilson’s disease. This is an autosomal recessive disorder associated with copper accumulation in the liver, basal ganglia and other organs. Several cases of Wilson’s disease have been reported in Thailand. The diagnosis should be considered in any patient who presents with extrapyrimidal or psychiatric disturbance before the age of 40 years. The specific Kayser–Fleischer (KF) ring is present in virtually 100% of patients with neuro-psychiatric Wilson’s disease. The diagnosis is usually based on abnormal biochemical findings including low serum caeruloplasmin, excess urinary copper excretion and high hepatic copper content. Serum caeruloplasmin was normal and KF rings were not found in our patients.

Conclusions

This is a descriptive study of a group of familial Parkinson’s disease. The clinical features are indistinguishable from typical PD. Normally, the diagnosis of PD is based on typical features; with time and repeated assessment, the accuracy of the diagnosis is increased. PD can be misdiagnosed, if the clinical symptoms develop in younger individuals or at an early stage of disease or with atypical symptoms. However, familial PD can be recognised by obtaining a complete family history and a family tree diagram. The results of this study demonstrate the usefulness of the family tree in the primary care setting. With this simple and inexpensive tool, we established the possibility of heritable disease and the likely mode of transmission. Furthermore, the information can also be used for genetic counselling of the affected family.

Even though familial PD is mainly found in Caucasian populations, this study showed that familial PD, although less prevalent, can also be found in South East Asia. Moreover, this study indicated there...
might be specific genetic transmission for certain ethnicity. For our study subjects, autosomal dominant transmission was the likely mode of inheritance. Since family members displayed different degrees of symptoms and signs, the PD gene may exhibit variable penetrance. However, our results are not conclusive due to gaps in the medical record of other relatives, and lack of genetic studies.

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REFERENCES

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**CONFLICTS OF INTEREST**
None.

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