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Review

Rapidly progressive familial parkinsonism with central hypoventilation, depression and weight loss (Perry syndrome)—A literature review

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Abstract

Autosomal dominant parkinsonism, hypoventilation, depression and weight loss (Perry syndrome) has been reported in only seven families worldwide. It is a rapidly progressive disease leading to death from respiratory insufficiency within a few years. Parkinsonism is usually mild, with bradykinesia, rigidity, rest and postural tremor, and axial signs. Response to levodopa is poor although transient response has been occasionally observed. The early signs include parkinsonism, depression and weight loss, whereas hypoventilation is a late feature. Neuropathology shows severe neuronal loss in the substantia nigra, less prominent neuronal loss in the locus coeruleus, and no or few Lewy bodies. In this review, we also propose diagnostic criteria for this condition.

Keywords: Hypoventilation; Familial; Genetic; Parkinsonism; Depression; Perry; Weight loss

Contents

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1. Introduction

The association of parkinsonism, hypoventilation and depression was first recognized in two unrelated Canadian families, and reported by Perry et al. in 1975 and then by Purdy et al. in 1979 [1–3]. Since then, only five additional kindreds have been described in Japan, France, the United Kingdom, the United States (of Irish descent) and Turkey [4–8,9,10]. No sporadic cases have been identified so far. Typical presentation includes moderate parkinsonism, apathy and depression, progressive weight loss, and central respiratory failure. The response to levodopa is usually poor. Although the clinical manifestations may vary, the evolution is relentless, ultimately leading to death within a few years.

In this article, we review the available clinical and pathological data, with the aim of bringing this rare and probably underdiagnosed condition to the parkinsonian community. We hope that studying rare conditions such as Perry syndrome will help us understand more common neurodegenerative diseases. We also propose diagnostic criteria for this condition.

2. Genealogical studies, known kindreds and mode of inheritance

In the seven families reported so far, the disease follows an autosomal dominant transmission pattern with a high penetrance (close to 50 percent affected subjects among the offspring). The pedigrees are small, with 2, 5, 5, 5, 6, 8 and 10 affected subjects spanning 2–3 generations. Among the 42 patients described, there is a moderate male predominance with 26 males and 16 females (male to female ratio, 1.6). This proportion is comparable to the one found in both sporadic and familial Parkinson disease (PD). The distribution of Perry syndrome is worldwide, with families in North America (Canada and the United States), Western Europe (France and the United Kingdom) and Asia (Turkey and Japan).

3. Clinical features

The cardinal symptoms of Perry syndrome consist of:

- autosomal dominant parkinsonism,
- hypoventilation,
- depression, apathy, social withdrawal and suicidal attempts,
- weight loss.

They will be discussed in the present section, along with the clinical course.

3.1. Age of onset and initial symptoms

The age of onset ranges from 30 to 56 with a mean of 46 ± 6.6 (years $\pm$ SD) in the 30 patients for whom this information is available (Table 1). The initial symptoms are either psychiatric or motor, often with weight loss. Most of the patients display progressive slowing of movements, together with a depressive or apathetic mood. In the French family [5,6], the disease began with parkinsonism in two patients, with personality changes in five, and with parkinsonism and personality changes in one. In the Japanese family, the presenting symptom was parkinsonism alone in two patients, and parkinsonism combined with depression in three [8], whereas in the family from the United Kingdom, parkinsonism was the presenting symptom in three patients [7]. In the West Virginia family, three patients presented with parkinsonism, one with parkinsonism and depression, one with severe weight loss, and one with depression and apathy [4]. In the other families, apathy, depression and lethargy preceded parkinsonism [1,2,9].

3.2. Parkinsonism

Parkinsonism has been described in every known patient with Perry syndrome (Table 1). All the cardinal signs of parkinsonism occur, including bradykinesia, rigidity, resting tremor and changes in postural reflexes. Two patients presented with postural tremor alone or in combination with rest tremor [3,8]. The features originally described by Perry et al. include masked facies, axial rigidity (stiff axial posture) with tremor appearing late in the disease; however, limb rigidity and limb bradykinesia were absent [1]. In most of the patients, parkinsonism is described as mild, although it may occasionally be severe (case III-4 of the second Canadian family [3]). Whereas in some families parkinsonism tends to present as a predominantly axial akinetic-rigid type, rigidity may also predominate in the limbs, with asymmetric tremor.

The response to levodopa ranges from no response [1–3] to significant improvement in some patients [4,5,7–9]. Any response is not usually sustained, disappearing over a period of a year [5,8]. Motor fluctuations and dyskinesia have been described in several patients, including lower limb dyskinesia and "on–off" phenomenon [3,5,8]. The following medications have been reported to have a mild beneficial effect in single patients: apomorphine [7], selegiline [7] and trihexyphenidyl [8]. Amantadine [1] and bromocriptine [6] were ineffective. One patient worsened following the administration of haloperidol [8].