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Emerging parkinsonian phenotypes

Phénotypes émergents de parkinsonisme

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ABSTRACT

There is no unique way to define Parkinson's disease (PD) clinically. "Classical parkinsonian features" can be found not only in sporadic idiopathic PD patients, but also in other parkinsonian disorders, such as genetic forms associated with mutations in PARK or in other genes. The present review will describe the parkinsonian phenotypes emerging from the new Mendelian genes which have been linked to PD (such as PARK9 and PARK14), the associated dystonia-parkinsonism disorders (such as the syndromes of neurodegeneration with brain iron accumulation) and the emerging data on heterozygous variants of genes which could influence the risk to develop PD and the PD phenotypes (like PD associated with glucocerebrosidase mutations).

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R É S U M É

Il n'existe pas de définition clinique univoque de la maladie de Parkinson (MP). Si les patients atteints de la MP idiopathique sporadique peuvent présenter des « signes classiques » de parkinsonisme, ceux-ci s'observent également dans d'autres contextes cliniques dont certaines maladies associées aux mutations génétiques (PARK ou autres gènes). Cet article est une mise au point des phénotypes parkinsoniens émergents associés aux nouveaux gènes mendéliens liés à la MP (PARK9, PARK14...), des syndromes dystonie-parkinson (syndromes neurodégénératifs associés à une surcharge cérébrale en fer) et des données nouvelles sur les variantes hétérozygotes de gènes ayant une influence potentielle sur le risque de MP et les phénotypes MP comme la MP associée aux mutations de la glucosé-
 brosidase.

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1. Abbreviations

CP ceruloplasmin
 FTL ferritin light chain

GBA glucocerebrosidase
 HARP hypoprebetalipoproteinemia acanthocytosis retinitis pigmentosa and pallidal degeneration
 INAD infantile neuroaxonal dystrophy

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KRD	Kufor-Rakeb disease
NAD	neuroaxonal dystrophy
NBIA	neurodegeneration with brain iron accumulation
PANK2	pantothenate kinase 2
PD	Parkinson's disease
PKAN	pantothenate kinase-associated neurodegeneration
PLA2G6	phospholipase A2 group VI
PLAN	PLA2G6 gene associated neurodegeneration
DLB	dementia with Lewy bodies
ACP	aceruloplasminemia

2. Introduction

PD is typically characterized by “classical parkinsonian features”, that are phenomenologically defined as the presence of akinetic-rigid syndrome with bradykinesia (slowness of movement), hypokinesia (poverty of movement, and movements that are smaller than intended), progressive fatiguing and decrement of repetitive alternating movements, increased muscle tone across a joint due to rigidity, resting tremor and postural instability (Abdo et al., 2010). Not all these features are considered mandatory. Despite existing diagnostic criteria (Gelb et al., 1999; Hughes et al., 1992), there is no unique way to define PD clinically. Furthermore, there is consensus that clinical syndromes dominated by levodopa-responsive parkinsonism without addition of uncommon features and with the frequent development of motor complications after several years of levodopa therapy should be considered typical.

“Classical parkinsonian features” can be found not only in sporadic idiopathic PD patients, but also in other parkinsonian disorders, such as genetic forms associated with mutations in PARK or in “other-than-PARK” (e.g. DYT) genes (Klein et al., 2009). Table 1 lists PARK and DYT1 monogenic forms associated with prominent parkinsonian features. Typical or atypical parkinsonian features can also be observed in genetic disorders usually characterized by prominent nonparkinsonian phenotypes, such as Gaucher's disease, Wilson's disease or pantothenate kinase-associated neurodegeneration. In addition to these, polymorphic variants in several susceptibility genes are considered to influence the development of PD features in patients who do not carry mutations in major PD genes. Thus, it is possible that PD is determined by the effects of genetic variants that are also common in the population. Indeed, it has been repeatedly observed that PD patients may carry single heterozygous variants in autosomal recessive PD genes, suggesting that these variants may constitute a risk factor for PD (Marongiu et al., 2008). The pathogenic role of heterozygous variants in autosomal recessive PD genes is currently debated, as these variants are occasionally found also in healthy controls. While the existence of a second, unidentified pathogenic variant in the same or in a distinct gene cannot be excluded, it remains possible that heterozygous variants could influence the risk to develop PD or the PD phenotype within a complex genetic and environmental background determining variable expressivity (Klein et al., 2007).

The present review will describe the phenotype emerging from the new Mendelian genes which have been linked to PD (the PARK loci: OMIM entry #168600), the associated dystonia-parkinsonism disorders and the emerging data on

heterozygous variants of genes which could influence the risk to develop PD and the PD phenotypes.

3. New phenotypes

3.1. Parkinson's disease associated with glucocerebrosidase mutations

The GBA gene is known to be deficient in patients with Gaucher's disease. This is a rare recessive disorder (GBA: OMIM #230800, *606463) resulting in a broad spectrum of neurological and nonneurological manifestations, including hepatosplenomegaly, anemia, thrombocytopenia, bone disease (Martins et al., 2009). Neurological manifestations affect only approximately 5% of patients with the homozygous form of Gaucher's disease (Martins et al., 2009), whereas parkinsonism affects only 2% of patients (Kraoua et al., 2009). The phenotype of parkinsonism in Gaucher's disease is that of an early-onset motor disorder, with inadequate response to levodopa and signs of cortical dysfunction (Kraoua et al., 2009). Furthermore, patients with Gaucher's disease display alpha-synuclein immunoreactive Lewy bodies resembling the pathological features observed in idiopathic PD (Wong et al., 2004).

A recent finding is that carriers of a single heterozygous GBA mutation, who are not affected by Gaucher's disease, present significantly increased risk of developing PD (Sidransky et al., 2009). GBA mutations have also been associated with a spectrum of parkinsonian phenotypes ranging from a classical PD phenotype to a DLB phenotype (Goker-Alpan et al., 2008). Indeed, a high prevalence of GBA mutations was reported among pathologically defined DLB patients (Goker-Alpan et al., 2006). In addition, GBA mutations have been proposed as a useful marker for Lewy body disorders (Clark et al., 2009). This has generated a considerable interest leading to further explore the relationship between the GBA gene and the associated phenotype in parkinsonian syndromes.

Clinical data of PD patients who carry GBA mutations are scarce. Among Ashkenazi patients, the symptom profile has been described to be similar to that of noncarriers although in mutation carriers, a younger age at onset (Aharon-Peretz et al., 2004), a lower frequency of symptoms asymmetry and of tremor has been described (Aharon-Peretz et al., 2005). In the largest series, mostly consisting non-Ashkenazi patients, mutation carriers have a lower frequency of asymmetric onset, resting tremor, bradykinesia, and rigidity (Sidransky et al., 2009). Analysis of nonmotor features revealed a possible higher frequency of cognitive changes in carriers (Sidransky et al., 2009), which are detected in about half of the patients (Neumann et al., 2009). Apart from a brief mention that orthostatic hypotension has the same frequency in carriers and noncarriers, autonomic features have not been investigated in detail.

Notwithstanding these pioneering insights into the role of GBA heterozygosity for apparently sporadic PD cases, many aspects remain to be addressed. First, it is not clear which is the phenotype of PD patients who carry GBA mutations. Some relevant clinical issues remain to be understood, such as

Table 1 – PARK, DYT and other main genotypes associated with prominent parkinsonism.
PARK DYT et autres génotypes principaux associés au parkinsonisme.

Disease (OMIM)	Map position	Gene	Transmission	PD phenotype	Main associated movement disorder
<i>PARK coding</i>					
PARK1/4 (163890)	4p21	SNCA	AD	Common	Typical PD with prominent non motor syndrome
PARK2 (600116)	6q25-q27	<i>Parkin</i>	AR	Common	Early onset parkinsonism, dystonia
PARK3 (602404)	2p13	Unknown	AD	Common	Typical PD
PARK5 (191342)	4p14	UCHL1	AD	Common	Typical PD
PARK6 (605909)	1p35-p36	<i>Pink1</i>	AR	Common	Typical PD
PARK7 (606324)	1p36	DJ1	AR	Common	Early onset parkinsonism, psychosis
PARK8 (607060)	12q12	LRRK2	AD	Common	Typical PD, benign course
PARK9 (606693)	1p36	ATP13A2	AR	Common	Kufor-Rakeb disease
PARK10 (606852)	1p32	Unknown	AD	Common	Variable
PARK11 (607688)	2q37	GIGYF2	AD	Common	Typical PD
PARK12 (300557)	Xq21-q25	Unknown	X-linked	Common	Variable
PARK13 (610297)	2p12	<i>Omi/HTRA2</i>	?	Common	Typical PD?
PARK14 (256600)	22q13	PLA2G6	AR	Common	Early onset dystonia-parkinsonism, myoclonus, epilepsy
PARK15 (605648)	22q12	FBXO7	AR	Common	Early-onset parkinsonism and pyramidal tract signs
PARK16 (613164)	1q32	Unknown	?	Common	Typical PD?
<i>DYT coding</i>					
DYT3 (314250)	Xq13	TAF1	X-linked	Common	Dystonia-parkinsonism
DYT5 (128230)	14q22	GCH1	AD	Common	Dopa-responsive dystonia
DYT12 (128235)	19q12-q13.2	ATP1A3	AD	Common	Rapid onset dystonia parkinsonism
DYT16 (612067)	2q31.3	PRKRA	AR	Common	Dystonia-parkinsonism
<i>Other coding</i>					
CHAC (200150)	9q21	VPS13A	AR	Common	Chorea, orofacial dyskinesias, parkinsonism
GD (606463)	1q21	GBA	AR	Exceptional	Both typical PD or atypical parkinsonism
HD (143100)	4p16.3	IT-15	AD	Common	Chorea, parkinsonism
PKAN (234200)	20p13	PANK2	AR	Uncommon	Dystonia
SCA2 (183090)	12q24	ATXN2	AD	Uncommon	Progressive cerebellar ataxia, dopamine-responsive parkinsonism
SCA3 (109150)	14q24.3-q31	ATXN3	AD	Uncommon	Progressive cerebellar ataxia, dystonia
SCA17 (607136)	6q27	TBP	AD	Uncommon	Progressive cerebellar ataxia, chorea, dystonia
WD (277900)	13q14.3-q21.1	ATP7B	AR	Uncommon	Tremor, dystonia

AD: autosomal dominant; AR: autosomal recessive; CHAC: choreoacanthocytosis; HD: Huntington's disease; PD: Parkinson's disease; PKAN: pantothenate kinase-associated neurodegeneration; SCA: spinocerebellar ataxia; WD: Wilson's disease.

dopaminergic responsiveness, the occurrence and phenomenology of motor complications, the frequency and severity of nonmotor symptoms. Another unaddressed issue is the long-term efficacy and safety of medical and surgical treatment of GBA carriers, their best medical management, their response to continuous infusion of dopaminergic agents and to deep brain stimulation. Finally, it remains unclear whether there is a common phenotype associated with GBA mutation carriers or if different mutations can lead to different phenotypes.

3.2. Neurodegeneration with brain iron accumulation

NBIA encompasses a group of progressive movement disorders characterized by iron accumulation in the brain. The term NBIA, now widely used, is sufficiently broad to encompass the spectrum of disorders previously called Hallervorden-Spatz syndrome as well as additional disorders with high brain iron content. The term NBIA is now favored as

an overarching term for the growing number of disorders contained therein, which encompass both typical phenotypes with infantile onset, and atypical phenotypes with adult onset. Fig. 1 summarizes the variety of disorders associated with NBIA.

3.2.1. Pantothenate kinase-associated neurodegeneration

PKAN is a rare autosomal recessive disease caused by mutations in the PANK2 gene on chromosome 20p13 (OMIM 234200), which encodes pantothenate kinase, an essential regulatory step in coenzyme-A biosynthesis (Leonardi et al., 2007). Patients with PKAN have dystonia, dysarthria, rigidity, pigmentary retinopathy and iron accumulation in the brain (Gregory et al., 2009). Atypical or uncommon phenotypes have been described (Marelli et al., 2005; Pellecchia et al., 2005). Brain MRI shows iron deposits (visible as pallidal hypointensity), best detected using T2*-weighted MRI. The combination of such hypointensity with a central hyperintensity (probably

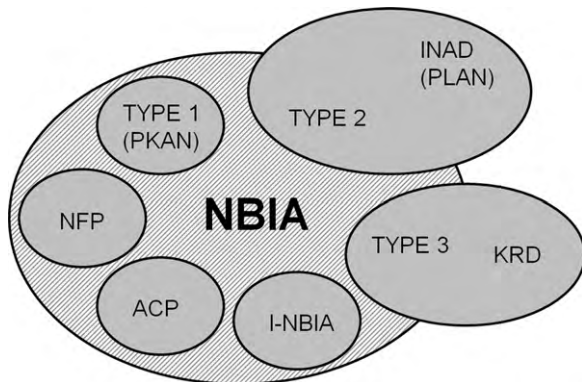


Fig. 1 – Neurodegeneration with brain iron accumulation (NBIA) encompasses several nosologic forms: “NBIA type 1”, also called pantothenate kinase-associated neurodegeneration (PKAN), is related to the presence of PANK2 gene mutations and associated with the “eye of the tiger” sign; “NBIA type 2” refers to PLA2G6 gene associated neurodegeneration (PLAN), which have been associated with infantile neuroaxonal dystrophy (INAD). The term “NBIA type 3” was recently introduced to indicate patients affected by Kufor-Rakeb disease (KRD) who also present brain iron accumulation. NBIA encompass other rare genetic disorders, such as aceruloplasminemia (ACP) and neuroferritinopathy (NFP). Finally, idiopathic forms (I-NBIA), likely caused by as yet undiscovered genes, have been described. PLAN and KRD are only partially included into the NBIA set, because these disorders can also present without evidence of iron accumulation in the brain.

La neurodégénérescence avec accumulation de fer dans le cerveau (NBIA) correspond à plusieurs formes nosologiques : la NBIA de type 1, également appelée la neurodégénérescence associée à la pantothénate kinase (PKAN), est liée à la présence de mutations du gène PANK2 et associée au signe d’œil de tigre ; la NBIA de type 2 se réfère à la neurodégénérescence liée au gène PLA2G6 (PLAN), que l’on a associé à la dystrophie axonale infantile (INAD). La NBIA de type 3 d’introduction récente correspond au syndrome de Kufor-Rakeb (KRS) où l’on trouve aussi une surcharge en fer dans le cerveau. La NBIA englobe d’autres troubles génétiques comme l’acéruloplasminémie (ACP) et la neuroferritinopathie (NFP). Enfin, des formes idiopathiques (I-NBIA), dont l’origine génétique probable n’est pas démontrée, sont décrites. La PLAN et le KRS peuvent se présenter sans accumulation de fer dans le cerveau et donc ne sont pas toujours des NBIA.

representing fluid accumulation or edema) is referred to as “eye of the tiger” sign (Sethi et al., 1988) which is highly correlated with the genetic status and the presence of PANK2 mutations (McNeill et al., 2008). Concentration of striatal dopamine reuptake transporters, as measured by dopamine transporter SPECT scan, have been reported to be normal in patients with PKAN (Cossu et al., 2005).

Classic PKAN is characterized by early onset and rapid progression (Gregory et al., 2009). The mean age of onset is around 3 to 4 years; in almost 90% of cases, onset occurs before

age 6 (Schneider et al., 2009). Affected children often are considered “clumsy” before onset of frank symptoms, which usually encompass gait or postural difficulties, with lower limb dystonia in about three quarters of patients (Hayflick et al., 2003; Schneider et al., 2009). Affected children usually lose the ability to ambulate by 10 to 15 years after disease onset. The patients tend to experience episodes of rapid decline interspersed with longer periods of relative stability. Some children have developmental delay, which is primarily motor, but sometimes global. The phenotype is nearly always characterized by generalized dystonia with often prominent oromandibular involvement (Schneider et al., 2006) dysarthria, akinetic-rigid parkinsonism and chorea may be present (Hayflick et al., 2003; Schneider et al., 2009). Pyramidal signs (spasticity, hyperreflexia, extensor toes) develop in about a quarter of patients (Hayflick et al., 2003). Corticospinal tract involvement leads to spasticity, hyperreflexia, and extensor toe signs. Cognitive features with behavioral changes, e.g. obsessive compulsive behavior, aggression, or depression, followed by dementia are seen in a third of patients (Marelli et al., 2005). In the later disease stages, patients frequently require tube feeding due to dysphagia. Gastroesophageal reflux and constipation can become chronic problems in advanced disease. Death typically occurs from secondary complications, including aspiration pneumonia and malnutrition. More rarely, patients die during uncontrollable episodes of status dystonicus (Gregory et al., 2009). Acanthocytes may be observed (Hayflick et al., 2003). Since the discovery of PANK2, it has been established that the association of HARP falls within the PKAN spectrum (Ching et al., 2002). Pigmentary retinal degeneration has long been recognized as a prominent symptom and clinical or electroretinographic evidence of retinopathy was present in two third of patients with classic PKAN (Hayflick et al., 2003).

Less typical, later onset (in the 20 s or 30 s) has also been reported in PKAN patients. Speech difficulty is a frequent presenting sign in such cases (Gregory et al., 2009; Hayflick et al., 2003). Other presenting symptoms include mild gait abnormalities and prominent psychiatric symptoms, including depression, emotional lability, impulsivity, obsessive compulsive disorder, and tourettism. Less common presentations of motor signs in genetically identified PKAN patients include bulbar amyotrophic lateral sclerosis-like symptomatology (Vasconcelos et al., 2003), focal upper limb dystonia (Chung et al., 2008; Marelli et al., 2005) or pure akinesia (Molinuevo et al., 2003). Motor involvement is generally less severe than in typical cases and has a slower rate of progression with loss of ambulation occurring within 15 to 40 years of onset (Gregory et al., 2009). Retinopathy as demonstrated by electroretinography has been reported less commonly in atypical patients (Hayflick et al., 2003).

3.2.2. Infantile neuroaxonal dystrophy and atypical neuroaxonal dystrophy

INAD is characterized by axonal degeneration with distended axons (spheroid bodies) throughout the central nervous system, with spheroids also found in peripheral nerves (Aicardi and Castelein, 1979). INAD is inherited in an autosomal recessive trait and some individuals with INAD show high brain iron and are classified as NBIA type 2 (Morgan et al.,

2006). Until 2006, the diagnosis of INAD was established by clinical and pathologic findings alone, independently of the patient's genetic status. Since the discovery of the PLA2G6 gene on chromosome 22q13 (OMIM 256600, PARK14), which is now known to be associated with INAD, molecular genetic testing has been used to confirm the diagnosis and the term PLAN was introduced to indicate coincidence between genetic status and clinical diagnosis.

INAD encompasses classic and atypical forms. PLA2G6-encoded INAD provides the typical presentation: onset is in infancy and death occurs within a few years. The disease is characterized by progressive motor and mental retardation, cerebellar ataxia, marked truncal hypotonia, pyramidal signs and early visual disturbances with strabismus, nystagmus, and optic atrophy. Disease progression is rapid. Many affected children never learn to walk or lose this ability shortly after attaining it. Severe spasticity, progressive cognitive decline and visual impairment typically result in death during the first decade. Brain MRI shows iron accumulation in the medial and lateral portions of the pallidum, without an "eye of the tiger" sign. Another additional feature is early cerebellar atrophy on brain MRI (Gregory et al., 2008, 2009).

Atypical NAD can present with a phenotype that differs quite significantly from the infantile cases (Gregory et al., 2008), because of later onset (2–7 years) with ataxia and gait instability as the most frequent presentation, and milder progression. The course is fairly stable during early childhood and resembles static encephalopathy but is followed by neurologic deterioration between 7 and 12 years of age. Patients develop progressive dystonia, dysarthria and neuro-behavioral disturbances with impulsivity, poor attention, and emotional lability. Optic atrophy, nystagmus, tetraparesis, and seizures occur similarly to typical INAD. Karak syndrome has also been shown to be caused by mutations in the PLA2G6 gene and falls into the spectrum of atypical NAD (Mubaidin et al., 2003).

In addition to NAD, adult-onset cases of PLAN without brain iron on MRI were recently reported (Paisan-Ruiz et al., 2009). This syndrome is characterized by age at onset of 21 to 34 years, subacute onset of dystonia-parkinsonism, pyramidal signs, eye movement abnormalities, cognitive decline, and psychiatric features, whereas cerebellar features were absent. Patients presented good response to dopaminergic treatment, with early development of levodopa-induced dyskinesias. Brain MRI shows some cortical atrophy and white matter changes with absence of iron deposition.

3.2.3. Neuroferritinopathy

Neuroferritinopathy usually presents with progressive adult-onset chorea or dystonia and subtle cognitive deficits. The movement disorder involves additional limbs within 5 to 10 years and becomes more generalized within 20 years (Crompton et al., 2005). Parkinsonian features, such as rigidity or bradykinesia, are usually not prominent, although an akineto-rigid syndrome can predominate (Crompton et al., 2005) and parkinsonism is the presenting feature in 7.5% of patients (Chinnery et al., 2007). Concentration of striatal dopamine reuptake transporters, as measured by SPECT, has never been investigated. The majority of individuals develop orofacial action-specific dystonia related to speech. Frontalis

overactivity and orolingual dyskinesia are common. Cognitive deficits, behavioral issues, and dysphagia become major problems with time. The diagnosis of neuroferritinopathy is based on clinical findings including adult-onset chorea or dystonia and MRI or CT showing excess iron storage or cystic degeneration. Neuroferritinopathy is inherited in an autosomal dominant manner. FTL gene on chromosome 19q13 (OMIM 606159) is the only gene currently known to be associated with neuroferritinopathy (Curtis et al., 2001).

3.2.4. Aceruloplasminemia

ACP is characterized by iron accumulation in the brain and viscera. The clinical triad of retinal degeneration, diabetes mellitus, and neurologic disease is seen in individuals ranging from 25 years to ages older than 60. The neurologic findings of movement disorder (blepharospasm, grimacing, facial and neck dystonia, tremors, chorea) and ataxia (gait ataxia, dysarthria) correspond to regions of iron deposition in the brain. Individuals with ACP often present with anemia prior to onset of diabetes or obvious neurologic problems. Psychiatric disturbance includes depression and cognitive dysfunction in individuals older than 50 years (Miyajima, 2008). The disorder can display a marked intrafamilial phenotypic variability and parkinsonian features, mainly characterised by bradykinesia, may be present (Fasano et al., 2008). Characteristic MRI findings are abnormal low intensities reflecting iron accumulation in the brain (striatum, thalamus, dentate nucleus) and liver on both T1- and T2-weighted images.

ACP is caused by the absence of serum CP, a copper-containing ferroxidase, which catalyzes the oxidation of ferrous to ferric iron, a change required for the normal transportation of iron by plasma transferrin (Yoshida et al., 1995). ACP is inherited in an autosomal recessive manner. It is caused by mutations in the CP gene on chromosome 3q23 (OMIM 604290), which encodes CP. The diagnosis of ACP in a symptomatic individual is based on the absence of serum CP, low serum copper concentration, low serum iron concentration, high serum ferritin concentration, and increased hepatic iron concentration (Miyajima, 2008).

3.3. PARK9: Kufor Rakeb disease

A syndrome characterized by clinical signs and symptoms of severe parkinsonism, as well as evidence of cortico-spinal tract disease, was first described in a Jordanian kindred in the village of Kufor-Rakeb (Najim al-Din et al., 1994), from which it was termed KRD. Supranuclear upgaze paresis, and dementia were additional features seen in these individuals, similar to Davison's pallido-pyramidal syndrome. The clinical picture was further characterized and several new features were identified, including facial-facial-finger mini-myoclonus, visual hallucinations, and oculogyric dystonic spasms (Williams et al., 2005). Treatment with levodopa provided symptomatic improvement, with the emergence of peak-dose dyskinesias along progression of the disease. Initial MRI reports of a significant atrophy of the globus pallidus and the pyramids were not fully confirmed in later study which observed widespread atrophy equally involving the cortex, subcortex, and cerebellum (Williams et al., 2005). KRD is inherited in an autosomal recessive manner and caused by

mutations in ATP13A2 gene on chromosome 1p36 (OMIM 606693), which encodes a lysosomal five P-type ATPase (Ramirez et al., 2006). After the discovery of the gene, new studies have further characterized the phenotype of KRD. One sporadic case from Brazil had juvenile parkinsonism with no pyramidal signs or dementia (Di Fonzo et al., 2007). Furthermore, two patients carrying a missense mutation in single heterozygous state had young onset PD without atypical features, suggesting that heterozygosity may cause a milder typical phenotype. However, in contrast to this observation, heterozygous variants were not found to be significantly more frequent in PD patients compared to controls (Djarmati et al., 2009). Furthermore, neither ATP13A2 genetic variability nor quantitative gene expression in brain appeared to contribute to familial parkinsonism or sporadic PD (Vilarino-Guell et al., 2009). Recently, a patient, affected by KRD was described, who presented putaminal and caudate iron accumulation bilaterally in the brain (Schneider et al., 2010), suggesting that KRD could be included in the NBIA group of syndromes.

3.4. PARK15: FBXO7

A new syndrome characterized by early-onset, progressive parkinsonism and pyramidal tract signs, was first described in a large Iranian family (Shojaee et al., 2008). All patients exhibited pyramidal features (extensor toes, hyperreflexia, and spasticity) mainly restricted to lower limbs. Parkinsonism became evident 5 to 20 years after appearance of pyramidal signs. Inheritance is autosomal recessive, due to mutations in the FBXO7 gene on chromosome 22q12 (OMIM 605648). Two unrelated families, of Italian and Dutch descent, with PARK15 were recently reported (Di Fonzo et al., 2009). The phenotype consisted of early-onset, progressive parkinsonism and pyramidal tract signs. The parkinsonism exhibited varying degrees of levodopa responsiveness in different patients. Disease progression was slow, and all patients were still alive decades after symptom onset.

4. Conclusions

Monogenic parkinsonian syndromes provide a unique opportunity to review the parkinsonian phenotype, either in its classical appearance outside the typical sporadic idiopathic PD, or in its combination to other neurologic features to constitute complex phenotypes. These complex phenotypes display a limited variability, whereby parkinsonian features are mainly combined with dystonia, pyramidal or cerebellar signs. We have highlighted a number of clinical features that can be helpful to guide genetic testing leading to a molecular diagnosis. Beside these, an increasing number of genes involved in the classic PD phenotype have been identified. In the near future, a substantial number of studies will be dedicated to these genetic disorders and new phenotypes will be described, particularly for NBIA syndromes.

Conflict of interest statement

None.

R É F É R E N C E S

- Abdo WF, van De Warrenburg BP, Burn DJ, Quinn NP, Bloem BR. The clinical approach to movement disorders. *Nat Rev Neurol* 2010;6:29–37.
- Aharon-Peretz J, Badarny S, Rosenbaum H, Gershoni-Baruch R. Mutations in the glucocerebrosidase gene and Parkinson disease: phenotype-genotype correlation. *Neurology* 2005;65:1460–1.
- Aharon-Peretz J, Rosenbaum H, Gershoni-Baruch R. Mutations in the glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews. *N Engl J Med* 2004;351:1972–7.
- Aicardi J, Castelein P. Infantile neuroaxonal dystrophy. *Brain* 1979;102:727–48.
- Ching KH, Westaway SK, Gitschier J, Higgins JJ, Hayflick SJ. HARP syndrome is allelic with pantothenate kinase-associated neurodegeneration. *Neurology* 2002;58:1673–4.
- Chinnery PF, Crompton DE, Birchall D, Jackson MJ, Coulthard A, Lombes A, et al. Clinical features and natural history of neuroferritinopathy caused by the FTL1 460InsA mutation. *Brain* 2007;130:110–9.
- Chung SJ, Lee JH, Lee MC, Yoo HW, Kim GH. Focal hand dystonia in a patient with PANK2 mutation. *Mov Disord* 2008;23:466–8.
- Clark LN, Kartsaklis LA, Wolf GR, Dorado B, Ross BM, Kisselev S, et al. Association of glucocerebrosidase mutations with dementia with Lewy bodies. *Arch Neurol* 2009;66:578–83.
- Cossu G, Cella C, Melis M, Antonini A, Floris GL, Ruffini L, et al. [123I]FP-CIT SPECT findings in two patients with Hallervorden-Spatz disease with homozygous mutation in PANK2 gene. *Neurology* 2005;64:167–8.
- Crompton DE, Chinnery PF, Bates D, Walls TJ, Jackson MJ, Curtis AJ, et al. Spectrum of movement disorders in neuroferritinopathy. *Mov Disord* 2005;20:95–9.
- Curtis AR, Fey C, Morris CM, Bindoff LA, Ince PG, Chinnery PF, et al. Mutation in the gene encoding ferritin light polypeptide causes dominant adult-onset basal ganglia disease. *Nat Genet* 2001;28:350–4.
- Di Fonzo A, Chien HF, Socal M, Giraudo S, Tassorelli C, Iliceto G, et al. ATP13A2 missense mutations in juvenile parkinsonism and young onset Parkinson disease. *Neurology* 2007;68:1557–62.
- Di Fonzo A, Dekker MC, Montagna P, Baruzzi A, Yonova EH, Correia Guedes L, et al. FBXO7 mutations cause autosomal recessive, early-onset parkinsonian-pyramidal syndrome. *Neurology* 2009;72:240–5.
- Djarmati A, Hagenah J, Reetz K, Winkler S, Behrens MI, Pawlack H, et al. ATP13A2 variants in early-onset Parkinson's disease patients and controls. *Mov Disord* 2009;24:2104–11.
- Fasano A, Colosimo C, Miyajima H, Tonali PA, Re TJ, Bentivoglio AR. Aceruloplasminemia: a novel mutation in a family with marked phenotypic variability. *Mov Disord* 2008;23:751–5.
- Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. *Arch Neurol* 1999;56:33–9.
- Goker-Alpan O, Giasson BI, Eblan MJ, Nguyen J, Hurtig HI, Lee VM, et al. Glucocerebrosidase mutations are an important risk factor for Lewy body disorders. *Neurology* 2006;67:908–10.
- Goker-Alpan O, Lopez G, Vithayathil J, Davis J, Hallett M, Sidransky E. The spectrum of parkinsonian manifestations associated with glucocerebrosidase mutations. *Arch Neurol* 2008;65:1353–7.
- Gregory A, Polster BJ, Hayflick SJ. Clinical and genetic delineation of neurodegeneration with brain iron accumulation. *J Med Genet* 2009;46:73–80.
- Gregory A, Westaway SK, Holm IE, Kotzbauer PT, Hogarth P, Sonek S, et al. Neurodegeneration associated with genetic defects in phospholipase A(2). *Neurology* 2008;71:1402–9.

- Hayflick SJ, Westaway SK, Levinson B, Zhou B, Johnson MA, Ching KH, et al. Genetic, clinical, and radiographic delineation of Hallervorden-Spatz syndrome. *N Engl J Med* 2003;348:33–40.
- Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinicopathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181–4.
- Klein C, Lohmann-Hedrich K, Rogaeva E, Schlossmacher MG, Lang AE. Deciphering the role of heterozygous mutations in genes associated with parkinsonism. *Lancet Neurol* 2007;6:652–62.
- Klein C, Schneider SA, Lang AE. Hereditary parkinsonism: Parkinson disease look-alikes – an algorithm for clinicians to “PARK” genes and beyond. *Mov Disord* 2009;24:2042–58.
- Kraoua I, Stirnemann J, Ribeiro MJ, Rouaud T, Verin M, Annic A, et al. Parkinsonism in Gaucher's disease type 1: 10 new cases and a review of the literature. *Mov Disord* 2009;24:1524–30.
- Leonardi R, Rock CO, Jackowski S, Zhang YM. Activation of human mitochondrial pantothenate kinase 2 by palmitoylcarnitine. *Proc Natl Acad Sci U S A* 2007;104:1494–9.
- Marelli C, Piacentini S, Garavaglia B, Girotti F, Albanese A. Clinical and neuropsychological correlates in two brothers with pantothenate kinase-associated neurodegeneration. *Mov Disord* 2005;20:208–12.
- Marongiu R, Ferraris A, Ialongo T, Michiorri S, Soleti F, Ferrari F, et al. PINK1 heterozygous rare variants: prevalence, significance and phenotypic spectrum. *Hum Mutat* 2008;29:565–74.
- Martins AM, Valadares ER, Porta G, Coelho J, Semionato FJ, Pianovski MA, et al. Recommendations on diagnosis, treatment, and monitoring for Gaucher disease. *J Pediatr* 2009;155(Suppl. 1):S10–8.
- McNeill A, Birchall D, Hayflick SJ, Gregory A, Schenk JF, Zimmerman EA, et al. T2* and FSE MRI distinguishes four subtypes of neurodegeneration with brain iron accumulation. *Neurology* 2008;70:1614–9.
- Miyajima H. Aceruloplasminemia. 2003 (updated 2008). *Gene Reviews* [Internet Publication]: <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=acp> (last accessed on August 23, 2010).
- Molinuevo JL, Marti MJ, Blesa R, Tolosa E. Pure akinesia: an unusual phenotype of Hallervorden-Spatz syndrome. *Mov Disord* 2003;18:1351–3.
- Morgan NV, Westaway SK, Morton JE, Gregory A, Gissen P, Sonek S, et al. PLA2G6, encoding a phospholipase A2, is mutated in neurodegenerative disorders with high brain iron. *Nat Genet* 2006;38:752–4.
- Mubaidin A, Roberts E, Hampshire D, Dehyat M, Shurbaji A, Mubaidien M, et al. Karak syndrome: a novel degenerative disorder of the basal ganglia and cerebellum. *J Med Genet* 2003;40:543–6.
- Najim al-Din AS, Wriekat A, Mubaidin A, Dasouki M, Hiari M. Pallido-pyramidal degeneration, supranuclear upgaze paresis and dementia: Kufor-Rakeb syndrome. *Acta Neurol Scand* 1994;89:347–52.
- Neumann J, Bras J, Deas E, O'Sullivan SS, Parkkinen L, Lachmann RH, et al. Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. *Brain* 2009;132:1783–94.
- Paisan-Ruiz C, Bhatia KP, Li A, Hernandez D, Davis M, Wood NW, et al. Characterization of PLA2G6 as a locus for dystonia-parkinsonism. *Ann Neurol* 2009;65:19–23.
- Pellecchia MT, Valente EM, Cif L, Salvi S, Albanese A, Scarano V, et al. The diverse phenotype and genotype of pantothenate kinase-associated neurodegeneration. *Neurology* 2005;64:1810–2.
- Ramirez A, Heimbach A, Grundemann J, Stiller B, Hampshire D, Cid LP, et al. Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. *Nat Genet* 2006;38:1184–91.
- Schneider SA, Aggarwal A, Bhatt M, Dupont E, Tisch S, Limousin P, et al. Severe tongue protrusion dystonia: clinical syndromes and possible treatment. *Neurology* 2006;67:940–3.
- Schneider SA, Bhatia KP, Hardy J. Complicated recessive dystonia parkinsonism syndromes. *Mov Disord* 2009;24:490–9.
- Schneider SA, Paisan-Ruiz C, Quinn NP, Lees AJ, Houlden H, Hardy J, et al. ATP13A2 mutations (PARK9) cause neurodegeneration with brain iron accumulation. *Mov Disord* 2010;25:979–84.
- Sethi KD, Adams RJ, Loring DW, el Gammal T. Hallervorden-Spatz syndrome: clinical and magnetic resonance imaging correlations. *Ann Neurol* 1988;24:692–4.
- Shojaee S, Sina F, Banihosseini SS, Kazemi MH, Kalhor R, Shahidi GA, et al. Genome-wide linkage analysis of a parkinsonian-pyramidal syndrome pedigree by 500 K SNP arrays. *Am J Hum Genet* 2008;82:1375–84.
- Sidransky E, Nalls MA, Aasly JO, Aharon-Peretz J, Annesi G, Barbosa ER, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. *N Engl J Med* 2009;361:1651–61.
- Vasconcelos OM, Harter DH, Duffy C, McDonough B, Seidman JG, Seidman CE, et al. Adult Hallervorden-Spatz syndrome simulating amyotrophic lateral sclerosis. *Muscle Nerve* 2003;28:118–22.
- Vilarino-Guell C, Soto AI, Lincoln SJ, Ben YS, Kefi M, Heckman MG, et al. ATP13A2 variability in Parkinson's disease. *Hum Mutat* 2009;30:406–10.
- Williams DR, Hadeed A, al-Din AS, Wriekat AL, Lees AJ. Kufor Rakeb disease: autosomal recessive, levodopa-responsive parkinsonism with pyramidal degeneration, supranuclear gaze palsy, and dementia. *Mov Disord* 2005;20:1264–71.
- Wong K, Sidransky E, Verma A, Mixon T, Sandberg GD, Wakefield LK, et al. Neuropathology provides clues to the pathophysiology of Gaucher disease. *Mol Genet Metab* 2004;82:192–207.
- Yoshida K, Furihata K, Takeda S, Nakamura A, Yamamoto K, Morita H, et al. A mutation in the ceruloplasmin gene is associated with systemic hemosiderosis in humans. *Nat Genet* 1995;9:267–72.