

Review

## Movement disorders in Latin America

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### Abstract

The authors review some particularities of movement disorders (MDs) in the ethnically diverse population of Latin America. Although idiopathic diseases are evenly prevalent, access to treatment encounters difficulties that are worth discussing. Infectious-parasitic diseases observed throughout the continent occasionally present as MDs, and will be individually reviewed. Inherited MDs with regional foci of increased prevalence, particularly spinocerebellar ataxias, will also be considered. Whereas there is no treatment for genetic disorders, most of the other conditions are preventable or amenable to adequate treatment. Hope for better health standards for the Latin American population lies in profound social and political changes that are still to come.

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**Keywords:** Movement disorders; Latin America; South America; Central America; Secondary parkinsonism; Drug-induced parkinsonism; HIV; AIDS; Neurocysticercosis; Tuberculosis; Sydenham's chorea; Manganese; Spinocerebellar ataxias

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**1. Introduction**

Latin America encompasses South and Central America and includes Mexico, in North America. Most Latin American countries are Spanish-speaking, except for Brazil (Portuguese), Jamaica (English), and French Guiana and Haiti (French) and Suriname (Dutch). Some countries also have indigenous languages in small regions. The main division between the Spanish and Portuguese languages reflects the Treaty of Tordesillas in 1494, when Portugal and Spain delineated clear-cut borders for the invasion and expropriation of the ‘New World’ from the native population. That was the first wave of European colonization to the continent. In subsequent centuries, the whole continent received intermittent waves of immigrants from different backgrounds, usually leaving the Old World in times of war, recession or political repression, or involuntarily being taken from Africa in a cruel trade aimed at consolidating production. It is, therefore, clear that Latin

America has a population of heterogeneous genetic and cultural ancestry, with some of above-mentioned immigrations resulting in local pools of Italians, Germans, Poles, Portuguese, Ukrainians, Chinese and Japanese.

As a consequence of prevailing social inequities, countries of Latin America are marked by certain peculiarities in terms of disease, mainly concerning infectious and transmissible conditions. Hereditary diseases may also present with epidemiological features, by virtue of this multitude of genetic contributions (Fig. 1).

The purpose of this review is to analyze the occurrence of movement disorders (MD) in Latin American countries, either emphasizing focal clusters of increased disease prevalence or observations regarding universal conditions. A broader recent review of MD in the tropics is available for further reference [1]. For the purpose of this review, an online search for terms related to MD was conducted, on Health Sciences Literature of Latin America and Caribbean (LILACS) and MEDLINE. In the case of MEDLINE, findings were limited to Latin

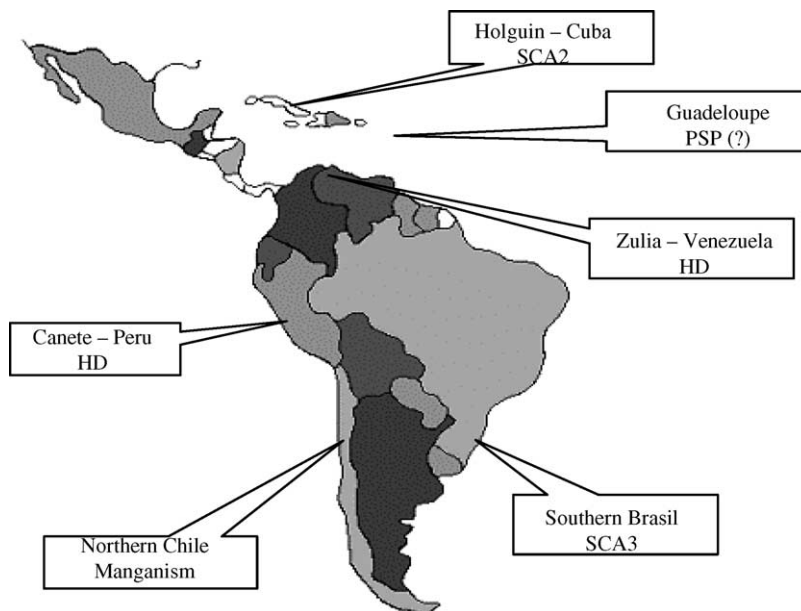


Fig. 1. Regions of Latin America where some MDs are particularly prevalent, either as a result of genetic or environmental factors (HD: Huntington’s disease; PSP: progressive supranuclear palsy; SCA2 and 3: spinocerebellar ataxias 2 and 3).

American data. We also included descriptions of cases from other continents, but regarding conditions largely known and prevalent in Latin America. Terms used for this search were: movement disorders, Parkinson's disease, parkinsonism, tremor, dystonia, tics, myoclonus, ataxia, chorea (and hemichorea), ballism (and hemiballism), hemichorea–hemiballism, infectious, HIV/AIDS, tuberculosis, cysticercosis, Sydenham's chorea, meningitis, encephalitis, drug-induced, and nutritional. There was no limit for date of publication for the research.

Literature findings were appraised according to disease etiology. After some remarks on MD by subtypes, subsequent topics are divided into infectious, environmental and hereditary conditions.

## 2. Idiopathic Parkinson's disease and parkinsonism

Data on epidemiological aspects of idiopathic Parkinson's disease (IPD) and parkinsonism (PK) are available from a number of countries in Latin America. The wide range of observed results, however, must be interpreted with caution. As a rule, these studies employ diverse diagnostic criteria and methods of statistical analysis, rendering results that cannot be compared. For instance, when individuals over the age of 40 are considered, the prevalence of IPD ranges from 286/100,000 in the rural region of the Andean cordillera in Bolivia [2] to 656.8/100,000 in Junín, Argentina [3]. This closely concurs with studies from developed countries [4,5]. In Medellín, Colombia, in the segment of population older than 50-years old, the prevalence of IPD is 176.4/100,000 and that of PK is 339.6 (IPD included) [6–8]. Latin American patients with IPD, even those coming from regions with a large indigenous population (Andean area), have clinical characteristics that are similar to those of cases reported elsewhere [9].

More than just a list of crude prevalence numbers, the epidemiology of PK from tertiary referral centers in Latin America draws our attention to the problem of drug-induced PK (DIP) (see below). In southeastern and southern Brazil, DIP is the second most common condition after IPD, accounting for 11.4 (Herdoíza, personal communication, 2005)–13.3% of all cases of PK [10]. Other etiologies are vascular PK (VP) (4.7%), progressive supranuclear palsy (PSP) (2%) and multiple system atrophy (MSA) (1.8%) (total parkinsonism-plus, 3.8%). Comparable results were found at different movement disorders centers, where parkinsonism-plus accounted for 6.1% of the cases of PK, whereas VP was present in 4.7% of cases (Herdoíza, personal communication, 2005). Very similar rates were found in a Colombian series of 302 parkinsonian patients, with a somewhat lower prevalence of DIP, of 5.4% [11]. These studies show that, with the exception of DIP, the rare forms of parkinsonism-plus also have low rates in Latin America.

Although vascular PK is shown within the wide prevalence ranges observed elsewhere [12,13], it is arguable that the main risk factors for vascular disease are not

properly treated in underdeveloped regions. It may be hypothesized that carefully designed studies would disclose an increased prevalence of modifiable vascular risk factors in association with parkinsonian symptoms.

*Parkin* gene mutations, inherited as an autosomal recessive trait, are the main cause of familial PD. They may also be responsible for a significant proportion of sporadic early-onset PD [14]. International collaborative studies evaluating European and South American patients have helped to shed light in the extent of *Parkin* mutations and their phenotype. The condition is characterized by earlier age at onset, as compared to non-*Parkin* cases [15–17], symmetrical PK and slower disease progression with favorable and sustained response to levodopa. Atypical findings included orthostatic tremor of the lower limbs [15], dystonia, hyperreflexia, axonal neuropathy, cerebellar ataxia and psychiatric manifestations [17].

*Treatment of IPD*—the high costs of adequate pharmacological treatment for IPD preclude the universal access of patients to these medications, and this is probably a problem shared by low-income patients from all over Latin America. Chaná and Galdames assessed the accessibility to pharmacological treatment of Chilean patients with IPD, and concluded that there was a direct relationship between family income, the frequency of visits to physicians, and the dose and cost of pharmacological therapy [18]. Because of the high cost of antiparkinsonian drugs, for some patients treatment starts up late, when patients are already experiencing significant disabilities in their daily living or professional activities [9]. Recently, Argentina approved a law for chronic disorders, including IPD, that grants a 70% subsidy to the costs of antiparkinsonian medication.

## 3. Dystonia

In general, there are no relevant differences in presentation of dystonic syndromes in Latin American movement disorders referral centers. Focal dystonia is more common than generalized types. The age at onset has a similar impact on prognosis, so that young patients with lower limb presentation evolve to generalized disease, whereas individuals older than 20 years at onset tend to maintain a pattern of focal disease [19].

In the genetic investigation of primary dystonia, 58% of 34 Argentinean patients proved to be positive for DYT1 mutations [20]. Secondary causes are found in 26–40% of patients with dystonia, and in this category tardive dystonia is more prevalent, followed by perinatal cerebral injury, cranio-cerebral trauma (CCT), stroke, Huntington's disease, encephalitis and Wilson's disease [21,22]. Patients with viral encephalitis may develop focal, segmental or generalized dystonia in the course of the acute illness [23] (Fig. 2, Dr Alarcón's patient). A highly unusual case of generalized dystonia secondary to Urbach–Wiethe disease (lipoid proteinosis) with striatal calcifications was recently reported [24].

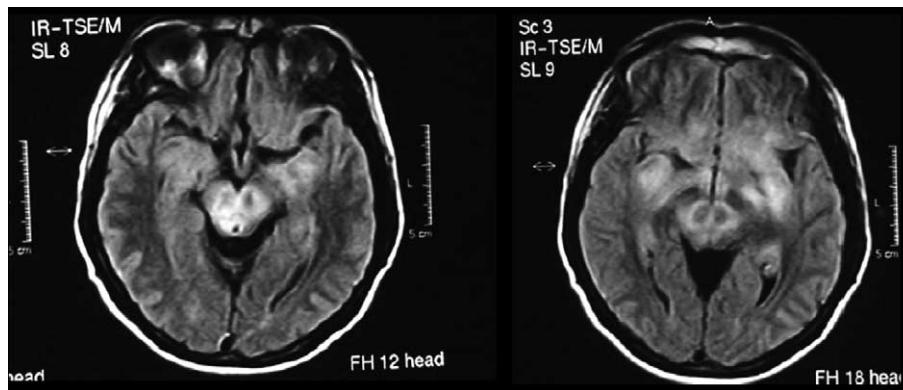


Fig. 2. MRI axial FLAIR images disclosing hyperintense lesions involving mesencephalic and diencephalic structures due to CMV infection, in a 25 years old immunocompetent male presenting with generalized dystonia.

Special forms of dystonia include L-dopa responsive dystonia (DYT5) [25,26] and paroxysmal dyskinesias (DYT 8 and 10). The latter have been widely reported in Latin America and seem no different from those reported elsewhere [27–29].

The burden and morbidity of focal dystonia have changed since the introduction of botulinum toxin in 1985. As expected, Latin American studies from specialized centers do not differ in terms of efficacy with botulinum toxin in the treatment of dystonia [22,30].

#### 4. Tics

Most cases of Tourette's syndrome (TS) are misdiagnosed or, what is more striking, correctly diagnosed but improperly treated. Reports from Argentina [31] and Chile [32] demonstrate that Tourette's syndrome (TS) in Argentina share remarkable similarities with cases reported elsewhere, thus confirming the universal cross-cultural uniformity. Patients from hospitals in Buenos Aires, whose inhabitants are mostly of European descent, included 34.6% Latins, 4% Jews, 3% Arabs and 1.3% Germans. Age at onset, tic features, male predominance and cephalocaudal progression showed no difference with European, American or Asian patients. Forty-eight out of 75 (64%) of these cases were initially interpreted as psychogenic and 62% had onychophagia, which has not been described in the literature [31]. Twenty-eight percent of patients had coprolalia, numbers variably found in other studies [33–34]. The most common foul words in the Argentinean series were 'dick' and 'cunt', which were expressed only partially. The River Plate Spanish versions of these words are 'pija' and 'concha', which have two syllables and sound more pungent than their English counterparts. Curiously, the term for 'fuck' ('coger') is seldom used perhaps because it ends as a consonant and, therefore, sounds weak [31]. Some patients with stuttering who present with adventitious facial movements during attempted speech are misdiagnosed as having Tourette syndrome (TS). The clinical picture of some

patients may represent a transition, some sort of missing link between TS and stuttering [35].

#### 5. Tremor

The prevalence of essential tremor (ET) was studied in Junín, province of Buenos Aires, by a two-phase method enabling the identification of probable cases by interview with later confirmation by clinical examination. The rates of raw prevalence for ET were 618.2 per 100,000 inhabitants (Melcon MO, Melcon CM, Micheli F, personal communication 2004). As for the treatment, a recent open-label, non-controlled trial suggested that controlled-release propranolol may be a helpful therapeutic option for the treatment of ET [36].

##### 5.1. Chin tremor

Hereditary chin tremor (HCT) or familial geniospasm has been regarded as an unusual autosomal-dominant condition characterized by recurrent episodes of involuntary oscillatory rhythmic movements of the chin muscles. Two families with HCT, one from Argentina [37] and another from Peru [38], have been reported in Latin America.

#### 6. Infectious-parasitic and autoimmune

The association of movement disorders with infectious-parasitic conditions is interesting from the therapeutic standpoint, since the former regularly deal with inexorable conditions while the latter may be amenable to treatment. In this context, a retrospective view over a large population of patients from a movement disorders unit in a tertiary hospital disclosed an infectious etiology in 1.4% of patients (14 individuals out of 1000) [39]. Hyperkinetic syndromes such as generalized myoclonus, myoclonus/ataxia, ataxia, hemichorea–hemiballism, Holmes' tremor and dystonia were more frequent (nine patients vs. five patients with

PK). Out of 14 patients, 10 patients had some reversible intercurrent underlying their neurological presentation, such as toxoplasmosis (secondary to AIDS or bone marrow transplantation), paracoccidioidomycosis, viral encephalitis and cysticercosis (cerebral aqueduct ependymitis leading to PK and ataxia secondary to basal cisterns racemous cysts). The four remaining individuals had untreatable conditions, such as HIV-related encephalopathy, subacute sclerosing panencephalitis and neurosyphilis.

### 6.1. HIV infection and AIDS

Neurological complications are common in advanced stages of AIDS. Movement disorders (MDs), however, are only seldom seen. This is illustrated in a retrospective evaluation of 2460 HIV-infected patients, in which 42.8% had some neurological complication and 1.13% (28 patients) developed MDs. Half of these individuals had PK, and most had HIV-related encephalopathy. Toxoplasmosis of the basal ganglia presented as hemichorea–hemiballism (HC–HB) in six subjects and hemidystonia in one. Other conditions observed elsewhere were generalized and spinal myoclonus, painful legs and moving toes syndrome, Holmes' tremor [40] and dystonic jerky hand in a patient with thalamic toxoplasmosis [41]. Whereas HC–HB in AIDS is usually the result of toxoplasmosis of the subthalamic nucleus, there is a single report of HC–HB secondary to cryptococcal granuloma [42]. A case with paroxysmal kinesigenic dyskinesias in a patient with encephalopathy due to HIV and another case with severe disabling motor restlessness of lower limbs as a result of myelopathy due to HIV have been observed (unpublished observations).

As a general rule, it may be stated that hyperkinetic movement disorders are the result of opportunistic infections, whereas hypokinetic signs most often correlate with HIV encephalopathy [43]. Nonetheless, in PK, reversible effects of antidopaminergic medications and treatable infections must be ruled out.

### 6.2. Meningitis

Pyogenic meningitis, a severe condition that is still endemic in Latin America, rarely leads to movement disorders. Chorea, tremor and PK were reported in other continents [44]. On the other hand, up to 16% of individuals with tuberculous meningitis (TBM) may develop involuntary movements. The most common abnormality is tremor (mainly postural), followed by PK, chorea and dystonia (both focal, lateralized or generalized). There is a poor correlation between neurological findings and focal lesions on imaging. Cerebrospinal fluid Ziehl–Nielsen and culture, ELISA, amino acid deaminase (ADA) and chest X-ray yield confirming results in only 50–60% of patients [23,45,46]. Hydrocephalus [47] and intracranial vasculitis leading to

basal ganglia infarcts [45] are likely physiopathological mechanisms.

One-third of cases of intracranial tuberculomas may be associated with movement disorders [48–50]. Chorea is the most common presentation, the others being dystonia, tremor and myoclonus. According to a recent series by Alarcón et al. a definite diagnosis of tuberculoma based on surgery, autopsy, CSF mycobacterial culture/AFB stain positive and findings in the CT scan or MRI images compatible with tuberculomas was established in 64% of patients. In 50% of them, there was anatomical correlation between an isolated lesion and the involuntary movement. In general chorea and dystonia correlate better with deep tuberculomas and tremor with cortical lesions [23,46,51]. Edema, direct pressure effect, ischemia and in some cases hydrocephalus are probably some of the mechanisms for movement disorders in intracranial tuberculomas. Two patients, one with chorea–ballismus and another with dystonia, had cerebellar tuberculomas [52]; the patient with chorea–ballismus had HIV. Both in the cases with tuberculous meningitis and in those with tuberculomas, the choreatic movements appear in the youngest patients [45].

Three patients with spinal tuberculous arachnoiditis had abnormal movements: two showed tremor and one had myoclonus [46]. In all the patients with tuberculosis of the CNS, the involuntary movements improved in a few weeks following antituberculous treatment [23,46,51].

### 6.3. Neurocysticercosis

Neurocysticercosis (NCC) is the most common helminthic infection of the central nervous system [53], particularly in areas of economic deprivation or regions where profitable swine farming is not associated with minimal sanitary standards [54]. The clinical symptoms of NCC depend on the location and number of parasites, and whether they are alive, degenerating or calcified. The most frequent presentation is seizures. However, a lower proportion of patients may present with increased intracranial pressure. In rare cases, hematogenous spread to spinal cord may lead to paraplegia [55]. In a Peruvian study employing MRI, basal ganglia infestation was detected in one quarter of individuals with NCC, mainly in those with five or more brain parasites [56]. No cases of MDs were detected. Since MRI does not detect calcifications, the extension of disease was probably underestimated.

In an Ecuadorian study, 15 patients (3.7%) who had developed movement disorders were selected from a descriptive observational prospective study with active symptomatic NCC [57]. The patients had more than 24 months of follow-up. Two patients had dystonia, four had tremor, eight PK and one chorea. The abnormal movement was focal in one third of patients and unilateral in 13.3% of the cases. In 87.5% of the patients with PK, the



extrapyramidal symptoms started bilaterally, and 46.6% of the patients had hydrocephalus. Chorea and dystonia correlated better with deep lesions and tremor with surface cysts. Parkinsonism was especially related to hydrocephalus, secondary to cysts of the IV ventricle, perimesencephalic cysts and basal racemous cysts. In some cases, PK was also surface cysts and ischemic lesions in the midbrain. All patients were administered antiparasitic treatment or underwent surgery. In 93.3% of the patients, the abnormal movement improved completely in weeks or months. One patient with slowly progressive PK continued to be administered L-dopa for up to 10 years after the diagnosis of neurocysticercosis and PK [57]. Parkinsonism with ataxia, myoclonus [58], hemichorea [59], tremor [60,61] and hemifacial spasm have also been described in the Americas and other continents [43,62]. Whereas cases of PK plus ataxia may anticipate a dismal prognosis [39], the majority of patients with PK recovered after antiparasitic treatment or surgery [23,58,60–62].

#### 6.4. Malaria

This is the leading cause of parasite-related mortality worldwide, particularly in children in sub-Saharan Africa [63]. Symptoms of CNS involvement are restricted to *Plasmodium falciparum* parasitism, occurring mainly in children under five years of age, young adults and non-immune travelers from non-endemic regions. The physiopathology of neurological disease is unclear, and a combination of mechanical (plugging of parasitized red cells in capillaries and venules) and humoral factors has been proposed [64]. In hyperendemic regions, the clinical setting of cerebral malaria is usually of sepsis, with hyperthermia (40–42 °C), metabolic acidosis and disturbances of consciousness evolving to coma. Seizures and cerebral hemorrhages may ensue. Dystonia, chorea or myoclonus may be observed in this critical period or following recovery. Parkinsonism has also been reported during acute stages of cerebral malaria and after

treatment with quinine [65]. There are also reports of ataxia during convalescence [64]. In general, movement disorders are self-limited complications of malaria and are less threatening than the underlying disease in itself.

#### 6.5. Paracoccidioidomycosis

Paracoccidioidomycosis (PCM) is seen after reactivation of latent forms of the dimorphic fungus *Paracoccidioides brasiliensis*. The disease is endemic in Latin America, particularly in middle-aged males of low socio-economic status [66]. There are also recent notifications from other continents [67]. CNS involvement in PCM (NPCM) is seen in 9.6–45% of patients with pulmonary disease, especially in those with disseminated disease [68]. Headache and hemiparesis are the most common presentations [69], but there are also cases of Holmes' tremor secondary to midbrain granuloma [70] and cerebellar ataxia (Fig. 3) [66,71]. Imaging findings are non-specific, showing multiple hypodense lesions with perilesional edema and contrast enhancement [69].

#### 6.6. Sydenham's chorea (SC)

A condition associated with low socio-economic and hygiene status, SC is part of the spectrum of rheumatic fever (RF). The clinical manifestations comprise chorea or hemichorea, behavioral disorders, dysarthria and muscular hypotonia. In RF and SC, group A  $\beta$ -hemolytic streptococcus (GABHS) elicits an immune response with production of antineuronal auto-antibodies that cross-react with the cytoplasm of caudate and subthalamic nuclei neurons [72,73]. Imaging studies may show increased volumes of the basal ganglia [74].

Sydenham's chorea is the main cause of chorea in pediatric patients [43]. In Minas Gerais, Brazil, approximately one quarter of 50 children with RF developed SC [72]. Average age at onset is 9 years, with female predominance of 1.3:1. Other than chorea, approximately

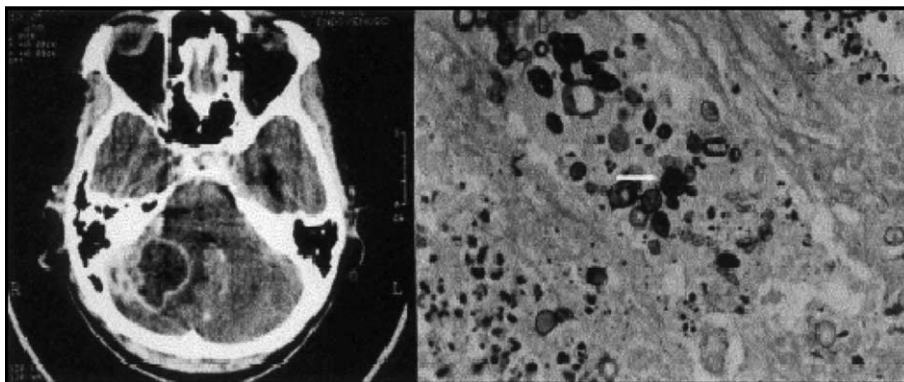


Fig. 3. (A). CAT scan showing right cerebellar hypodense lesion with ring contrast enhancement, suggestive of abscess. (B). Photomicrography of pathological analysis of surgical material disclosing yeast with multiple budding (arrow), compatible with *Paracoccidioides brasiliensis* (hematoxylin-and-eosin, 300 $\times$ ) (reprinted from da Silva et al., with permission).

60% of individuals may present muscular hypotonia, dysarthria and emotional lability. In 50% of patients, chorea may persist for over two years, particularly in girls and patients with carditis [75]. In this subset of patients refractory to conventional therapy (i.e. neuroleptics and valproic acid), steroids seem a promising alternative [76] and confirmatory studies are awaited. At a 3.5-year follow-up, 29–40% of patients may have relapse of chorea [72,77,78]. Benzathine penicillin is effective in the secondary prevention of further bouts of chorea in 70% of patients [78].

### 6.7. Prion disease

Two main reports give insight into the presence of prion-related disorders (PRD) in southern Latin America. In 1989, Taratuto et al. published their observations of 10 individuals from Argentina and Chile with Creutzfeldt–Jakob disease. All cases had postmortem confirmation diagnosis. Individuals from 42 to 63 years of age presented either with behavioral changes (five patients) or with differing combinations of movement disorders and cerebellar or pyramidal signs (five patients), later followed by dementia. EEGs disclosed periodic complexes in eight individuals. Disease course lasted from 3.5 to 24 months [79].

Creutzfeldt–Jakob Disease (CJD) has been widely reported in Chile. From 1931 to 1983, 87 cases of CJD had been ascertained; 39 cases were familial, accounting for 45% of the sample [80]. The high proportion of familial CJD observed in Chile is probably the result of both a genetically determined susceptibility to the CJD virus and a high degree of case ascertainment. These family cases are associated with the codon 200 mutation of the PRNP amyloid precursor gene on chromosome 20 [81].

Up to December 2003, there was a total of 69 defined PRD cases in Argentina, confirmed by autopsy findings, and the incidence for the previous year was 0.46 per million. Nine out of these 69 (13%) are familial cases (verified by molecular biology studies) (Somoza, personal communication 2005).

Familial PRD was reported with a singular phenotype of frontotemporal dementia. Instead of early myoclonus or cerebellar changes with cognitive impairment, most individuals presented with apathy, depression, disinhibition and executive dysfunction, with further development of motor symptoms. Out of 19 individuals who presumably had the disease, 12 were clinically assessed. Eight had PK and one myoclonus plus PK [82]. Mutation analysis disclosed a novel point mutation at the codon 183 of the prion protein gene [83].

### 6.8. Subacute sclerosing panencephalitis (SSPE)

Distinct neurological complications may be observed after measles infection, such as post-measles encephalitis

and inclusion body encephalitis, transverse myelitis and SSPE [84]. SSPE is still predictable in underdeveloped regions where the control of measles has only been recently attained, unlike industrialized countries, in which vaccination programs eradicated measles. Measles immunization itself, however, may be a cause of SSPE. The condition is due to permanent slow CNS infection with a defective RNA virus of paramyxoviruses. Incipient pathological changes in the nervous system appear with the primary infection. There is evidence that the measles virus loses the ability to express its envelope, and this could explain the difficulty of detecting serum antibodies in some individuals [85]. On pathological grounds, meningeal and parenchymal inflammation in the parieto–occipital region evolves to generalized gray and white matter gliosis, proliferation of astrocytes, perivascular cuffing and lymphocytic and plasma cell infiltration. Degeneration of oligodendrocytes may lead to extensive areas of demyelination.

There is a mean latency of 5–8 years from initial measles infection to SSPE. The younger the child when first infected, particularly under 1 year of age, the shorter the latency period. The period of incubation may also be shorter if SSPE follows immunization [86]. Behavioral and cognitive symptoms may be first noted in school. Alternatively, generalized tonic–clonic seizures may debut the clinical picture. Myoclonic jerks of the head and limbs then become evident, and may be a cause of periodic head drop or falls. With time, other movement abnormalities such as ataxia, dystonia and hyperkinesias may appear. Pyramidal signs are subsequently detected, whereas cognitive function progressively worsens. In advanced disease stages, autonomic impairment leads to abrupt temperature fluctuations [84]. In children, cognitive deterioration, myoclonus and a EEG suggest the possibility of SSPE; however, many cases are not easy to diagnose, especially in adults, in whom a past history of measles is harder to retrieve and who may present with atypical features, such as amaurosis and purely psychiatric features [87].

According to a retrospective nationwide study in Brazil, 25 definite cases of SSPE were diagnosed by pediatric neurologists from 1990 to 1996, and a further 23 individuals had probable or possible SSPE. In this sample, mean age at onset was 10 years old, with males more frequently affected. Most common initial presentations were myoclonus, tonic–clonic seizures, behavioral and learning disturbances and gait disorders. Half of the sample had a clear previous history of measles. Furthermore, over half of the samples were only diagnosed when the disease was at an advanced stage. Most EEGs disclosed periodic slow wave complexes. Twelve patients died as a consequence of the disease, and there was spontaneous remission of symptoms in two (diagnostic certainty level lacking) [88]. Even though possible misdiagnosis and limited follow-up are causes for skepticism about the data, this work gives an estimate that SSPE is still an endemic condition, and sporadic

outbreaks of measles may turn into future diagnoses of SSPE.

## 7. Environmental and lifestyle

### 7.1. Central and peripheral trauma

Cranio-cerebral trauma (CCT) is a major cause of death and permanent disability, especially in young individuals. Although no systematic evaluation of MD has been conducted in such a group of patients in Latin America, it is expected that data available from developed countries may at least be reproducible in these countries. Almost any kind of MD may be observed after CCT, more frequently after severe trauma [89]. In Germany, in a cohort of 221 patients previously admitted for CCT with an initial Glasgow Coma scale of 8 or less, 22.6% had some kind of transient or permanent MD. The most prevalent were an intentional/postural tremor of >4 Hz, kinetic/postural tremor of 2.5–4 Hz, focal dystonia or hemidystonia and PK [90].

Dystonia following peripheral trauma remains a controversial issue [91–93]. Since not even the pathophysiology of idiopathic dystonia is well understood, we accept an a priori reasoning on the existence of MD subsequent to traumatic injuries, as reported by Nobrega et al. [94]. In this series, one patient had upper limb focal dystonia after shoulder trauma, whereas two other individuals had choreoathetosis after cast immobilization and tremor secondary to traumatic loss of three fingers of a hand.

### 7.2. Drug-induced movement disorders (DIMD)

Drug-induced PK (DIP) is the second most common cause of PK in Brazilian movement disorders clinics [10]. Cinnarizine, flunarizine and haloperidol are the usual offenders. The first description of PK induced by calcium channel blockers employed in the treatment of vestibular disorders was made by De Melo-Souza in 1984. The clinical picture is one of symmetrical Parkinsonian signs and depression, mainly affecting elderly women [95]. This is of the utmost importance for the Latin American population, since in many of these countries flunarizine and cinnarizine are sold as over-the-counter medication to presumably treat dizziness of unspecified cause [96].

Drugs of different pharmacological classes have been ascribed as causative or worsening agents of PK, such as amiodarone [97], amlodipine [98], veralipride [99] and fluoxetine [100]. Flunarizine may be involved in tardive dyskinesia [101]. Such reports focus our attention on the potential of drugs used in different settings to interfere with motor control. It is important to keep an open mind on this possibility, since interactions not yet described may contribute to increasing morbidity in these patients. This

is of practical concern in the elderly population IPD, with frequent co-morbidities and long prescription lists.

A survey of 878 psychiatric in-patients chronically treated with antipsychotic drugs showed that 62% had tardive dyskinesia and 0.9% tardive dystonia. Tardive dyskinesia was significantly higher in females (69%) than in males (52%) and more common in schizophrenic patients [102].

*Adulterated DIMD:* A group of patients from Peru and Argentina developed unexpected DIMD that could not reasonably be attributed to any drug they were presumably taking. Patients presented with acute dystonic reactions or worsening of PK 1–2 weeks after starting a new medication. In both instances, a high degree of suspicion led to recheck the capsule or pill content, which was traced to the same factory lot in each case and found to be either watered down (in Argentina) or adulterated (in Peru). Unfortunately, adulteration or falsification of drugs is an ongoing occurrence in Latin America. These findings add a new and criminal dimension to the term iatrogenic movement disorders, as there is no evidence of an act of commission or omission by the physician. This report raises serious safety concerns and demands for improved active surveillance strategies, particularly at the nationwide multicenter level, by means of enhanced community awareness, implementation of permanent quality controls, and establishment of disciplinary actions for defaulters [103].

### 7.3. Exposure to toxins—occupational neurology

Parkinsonism secondary to environmental or occupational factors is a long-known fact. The question of whether urban or rural living entail any epidemiological risk in developing IPD has not been consistently answered and was addressed in the state of São Paulo, Brazil, where 118 IPD patients were analyzed according to their background. There were 71 individuals with a rural background and 47 urban dwellers. No differences were found between these groups regarding age at onset or clinical picture [104]. On the other hand, a case control study with IPD patients in the state of Rio de Janeiro showed increased exposure to cyanide, mercury and petroleum products in IPD patients, when compared to controls [105].

Chronic occupational exposure to manganese is known to induce PK with dystonic features, progressive course and a poor response to levodopa [106]. Brazil and Mexico are the world leaders in manganese production, and reports of manganese poisoning in miners are available from Argentina [107], Mexico [108] and Chile. In the last century, neuropsychiatric manifestations were well recognized in manganese miners, even by the population living nearby mines of Northern Chile [109]. Emotional lability, visual and auditory hallucinations and behavioral changes such as nervousness, irritability and compulsive acts were known in the community as *locura manganica* (manganese madness). These symptoms subsided in some weeks, giving



place to muscular weakness and rigidity, postural tremor, dysarthria, gait disorders and headache. Asymptomatic miners taken as controls also displayed cogwheeling phenomena as an isolated finding [109]. More recently, the main pathological findings in experimental models of manganism were described as gliosis and iron/aluminum deposition in the globus pallidus and substantia nigra *pars reticulata* [110].

Manganese-containing fungicides are associated with MDs in rural workers. Kindled by two cases of PK in young individuals exposed to maneb (manganese ethylene-bis-dithiocarbamate), Ferraz and coworkers evaluated 50 agricultural workers systematically exposed to this substance and found high rates of rigidity and cogwheel phenomena. Some of those individuals had symptoms similar to the miners in Chile described above [111].

In addition, regarding PK in environmental conditions, herbicides with glycine-derivates accidentally absorbed transdermally were involved in the subacute development of levodopa-responsive symmetrical PK [112]. The same holds true for industrial component *N*-hexane [113] and organophosphate insecticides [114].

The accidental or intentional intake of substances or drugs that are toxic for the nervous system may induce movement disorders. In Ecuador, two individuals developed movement disorders after attempting suicide-taking podophyllin, a substance used for the treatment of condyloma acuminatum. Following ingestion, the patients had rapid deterioration of consciousness into coma for the first 24 h. In the second and third weeks after ingesting the resin, dystonic, choreatic, and myoclonic movements appeared. Peripheral neuropathy also developed. In the most severely affected patient, involuntary movements persisted for more than a year thereafter. This toxin, which probably interferes with the neuronal metabolism or produces cytological disturbances such as mitotic arrest, exerts a severe impact on the central and peripheral nervous system, even when it is used chronically as a topical application [115].

#### 7.4. The parkinsonism complex of Guadeloupe

In a time when the *lytico-bodig* complex of Guam was gradually disappearing, Caparros-Lefebvre and Elbaz described a group of individuals in Guadeloupe, Caribbean French West Indies, with unexpectedly high prevalence of atypical PK [116]. Indeed, in an original sample of 87 patients, more individuals presented with atypical PK than with IPD (PSP, 31; atypical PK, 30; IPD, 22). Four patients also displayed motor neuron disease. Patients with PSP presented with early postural impairment and falls, gaze palsy, lack of response to levodopa, signs of frontal lobe dysfunction, pseudo-bulbar affect and dysarthria. Three autopsied cases of PSP had mesencephalic deposits of pathological tau protein [117]. The condition is probably related to consumption of derivatives of plants of the Annonaceae family. Compounds from Annonaceae were

shown to inhibit mitochondrial complex I [118] and to lead to dopaminergic neuronal cell death by inducing apoptosis [119]. Experimental cell death is decreased when exposure to the toxin is shorter [119] and, perhaps in parallel with that, some Guadeloupean patients have had partial improvement of parkinsonian symptoms after stopping the intake of such compounds [120]. There is definite similarity of clinical presentation between Guadeloupean cases and the ones previously reported in Kii peninsula (Japan) and Guam (Mariana Islands) [120], classical geographical clusters in which environmental factors were also raised as possible culprits.

## 8. Cerebrovascular disorders

Stroke, the commonest disabling and lethal neurological disease of adult life, is the most devastating manifestation of hypertension and atherosclerosis. A recent Ecuadorian study [121] systematically evaluated the clinical picture, topographical correlations, follow-up and frequency of movement disorders associated with stroke. Fifty-six patients (3.7%) who had developed movement disorders were selected from a prospective collected stroke data registry cohort. All the patients who had developed abnormal movements were followed up for at least one year after the onset of the movement disorders. Chorea, tremor, dystonia, and PK were found in these patients. As in other series [122], high blood pressure and heart disease were the principal stroke risk factors. Chorea was the most common movement disorder after stroke and appears in older patients. This study, which is one of the very few and largest prospective studies on post-stroke movement disorders, is difficult to compare with other studies since most reports are of isolated cases or series of patients with a given type of abnormal movement or anatomical lesion (see [121] for further details). This series shows that lesions involving the basal ganglia (but almost always with surrounding deep white matter) most commonly cause movement disorders. Correlations between site of lesion and type and laterality of movement disorder, however, are difficult to draw. Involuntary movements tend to persist despite the functional recovery of motor deficit [121].

## 9. Inherited movement disorders

### 9.1. Huntington's disease

The Venezuelan Huntington's disease (HD) kindreds were first described by Negrette and colleagues [123]. These kindreds now represent the largest and best characterized HD population in the world. The families primarily live in the region of Lake Maracaibo in Zulia state. Some dwell in the city of Maracaibo; others live in tiny, rural fishing villages around the lake. The Venezuelan kindreds are

highly heterogeneous. By and large, they are Hispanic, but their genetic and phenotypic heterogeneity results from matings with European sailors and traders and some Native American admixture. Most members of the Venezuelan kindreds are descendants of a woman living in the early 19th century in a stilt village on Lake Maracaibo. She died of HD and passed her abnormal allele through 10 generations.

Genetic and clinical data from the Venezuelan kindreds were responsible for localizing the HD gene on chromosome 4p16.3 [124] and for subsequently discovering the defective gene and identifying the nature of its mutation [125].

Since 1970, clusters of HD have been detected in Peru, with most affected individuals living in Canete [126], a valley 140 km from Lima, currently acknowledged as the second largest population of HD in the world, second to Maracaibo. The precise origin of the disease is unknown, but these patients are mostly half-bred from a mixture of Caucasian and natives rather than from a mixture of Chinese, Japanese or African–American [127,128].

## 9.2. Spinocerebellar ataxias

The inherited ataxias comprise a group of diseases in which cerebellar degeneration may occur in isolation or with multiple neurological signs, such as peripheral neuropathy, retinal degeneration, ocular movement disturbances, PK, pyramidal signs and dementia. The classification of autosomal dominant ataxia—referred to as spinocerebellar ataxia (SCA)—once based on clinical grounds, was improved by the identification of responsible mutations and potential chromosomal *loci*. Twenty-eight different SCAs have been described so far [129]. Nonetheless, SCAs' classification has been regularly reviewed, since new kindreds are constantly being reported.

Although SCAs are observed worldwide, some of their subtypes are unevenly spread, as is the case in Latin America. These are very slowly progressive diseases that in many cases start in the most productive period of an individual's life, and their occurrence in such an elevated proportion in some parts of the continent leads to a considerable negative psychological, familial and economic impact [130].

### 9.2.1. SCA3—Machado–Joseph disease

Machado–Joseph disease (MJD–SCA3) is particularly prevalent in the state of Santa Catarina, southern Brazil. This prevalence reflects the emigration from the Azores islands (Portugal) that took place about 300 years ago towards mainland Europe, Africa and the Americas. In South America, most Azoreans colonized southern Brazil.

The genetic basis for MJD is an abnormal expansion of a coding CAG trinucleotide in chromosome 14. Expanded CAG repeats is also the molecular genetic substrate in SCA 1, 2, 3, 6, 7 and 17 [129]. Silveira and co-workers studied a cohort of 92 unrelated SCA patients from United States,

Canada, Brazil, Portugal and India [131]. Subjects were screened for SCA1 to SCA5 and dentatorubropallidolusian atrophy (DRPLA). It was found that MJD was present in 41% of cases and 84% of Portuguese individuals, being the most common inherited ataxia. As a rule, individuals with Portuguese background had increased chance of harboring SCA3 mutation and a decreased probability of having any of the other SCAs or DRPLA.

An investigation of Brazilian patients with inherited ataxia was also conducted. In this study, 328 individuals from 90 families with different modes of inheritance had genetic analysis for SCA1, SCA2, SCA3 and DRPLA. Thirty-five families had some of the mutations, and 32 of these had an autosomal dominant pattern of inheritance (ADI). MJD was the most diagnosed condition, in 44% of subjects with ADI and 30% of the whole group. Out of all individuals with ADI, SCA1 and SCA2 accounted for, respectively, 6 and 9% of cases. No cases of DRPLA were found [132]. More recently, Teive and coworkers found even higher prevalence of MJD in 100 Brazilian families (70.7% of detected mutations). Other mutations were SCA 10 in 12.3% of families, SCA 2 in 7.7%, SCA 7 in 4.6%, SCA 1 in 3.0% and SCA 6 in 1.5% [133].

### 9.2.2. SCA 2

In 1971, Wadia and Swami in India made the first description of an autosomal dominant ataxia frequently associated with slow saccades, which is now recognized as SCA2 [134]. In a clinical context where ataxia is the main finding, SCA2 additionally displays slow saccades in 50–84% of patients, although formal ocular examinations may also disclose other abnormalities, such as gaze-evoked nystagmus, in a high proportion of patients [135]; retinal degeneration is rarely seen. Peripheral neuropathy and cognitive dysfunction mainly of frontal lobe type are also present to a higher extent than in other SCAs [129]. The disease is the consequence of expansion of CAG in chromosome 12.

In the province of Holguín in eastern Cuba, 125 families have been ascertained to have SCA2. This region has the highest prevalence of SCA2 worldwide, 43 cases per 100,000 inhabitants and an annual incidence of 4.39 new cases per 100,000 inhabitants. In the city of Baguanos, this prevalence reaches 503 cases per 100,000 inhabitants. Indeed, 70% of individuals in Cuba with SCA2 live in Holguín [136, 137]. As seen with other autosomal dominant diseases with high penetrance, this is probably the result of a founder effect, although it has not been possible to trace back the disease to its ancestors so far (L Velazquez-Perez, personal communication).

In SCA2, symptoms of cerebellar dysfunction may be preceded by changes in electroneuromyographic studies, disclosing patterns of peripheral neuropathy consistently related to the extent of CAG expansion. This was also subject of investigation by the Cuban group of Velazquez-Perez and colleagues, who found that individuals with more

than 41 expansions of CAG had total blockade of afferent conduction of axonal type. On the other hand, patients with less than 41 repeats had less severe neuropathy of variable patterns, mainly of demyelinating type [138].

### 9.2.3. SCA 10

A new syndrome of autosomal dominant ataxia has recently been ascertained as SCA10. In this inherited ataxia, a singular combination with epileptic seizures is seen in 25–80% of patients, depending on the pedigree [139]. Epilepsy may be complex partial or generalized in type. SCA10 is caused by expansion of a non-coding ATTCT pentanucleotide in chromosome 22, also displaying the phenomenon of anticipation [140]. The disease was initially identified in six families of exclusively Mexican descent. More recently, SCA10 was diagnosed in Brazil in eight additional families of Azorean and Indian ancestry. Of note is that all affected members presented pure cerebellar ataxia without epilepsy [141].

### 9.2.4. Other SCAs

In Argentina, 4 (7–3%) out of 55 patients screened for ataxia were positive for the SCA1 mutation, 9 (15.8%) out of 57 for the SCA2 mutation; 3 (5.8%) out of 563 and 1 (2.4%) out of 42 were positive for the SCA6 mutation [142].

## 10. Final remarks

The diagnosis of movement disorders in Latin American countries is not fundamentally different from other continents. The most common diseases display similar epidemiological figures. In the treatment of IPD and PK, most patients do not benefit from the same availability of medications, mostly due to economic factors. Furthermore, adulterated medications have been reported. Medications of doubtful efficacy and clear noxious potential, such as cinnarizine and flunarizine, must not be sold over the counter. Tuberculosis and AIDS are the most frequent infections causing MDs. Inherited MDs are rare, with remarkable foci of increased prevalence. It cannot be doubted that improved health standards rely on education and better sanitary standards for the entire Latin American population. With globalization (a new name for an old process), foreign interference consistently keeps on barring continental socio-economic development. It has become clear that globalization should not be promoted any further.

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