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QUEBEC COOPERATIVE STUDY
OF FRIEDREICH'S ATAXIA

The Natural History of Machado-Joseph Disease

An analysis of 138 personally examined cases

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ABSTRACT: We have examined 138 cases of a disorder previously described in people of Portuguese origin and which has received many names. By computer analysis of 46 different items of a standardized neurological examination carried out in each patient, we have been able to delineate the main components of the clinical presentation, to conclude that the marked variability in clinical expressions does not negate the homogeneity of the disorder, and to describe the natural history of this entity which should be called, for historical reasons, ***"Machado-Joseph Disease"***.

This hereditary disease has an autosomal dominant pattern of inheritance, presenting as a progressive ataxia with external ophthalmoplegia, and should be classified within the group of ***"Ataxic multisystem degenerations"***. When the disease starts before the age of 20, it may present with marked spasticity, of a non progressive nature but often so severe that it can be accompanied by "Gegenhalten" countermovements and dystonic postures but little frank dystonia. There are few true extrapyramidal symptoms except akinesia. When the disease starts after the age of 50, the clinical spectrum is mostly that of an amyotrophic polyneuropathy with fasciculations accompanying the ataxia. For all the other cases the clinical picture is a continuum between these two extremes, the main determinant of the clinical phenotype being the age of onset and a secondary factor, the place of origin of the given kindred. The ataxic and amyotrophic components are clearly progressive with time in contrast to the spasticity component. Although the majority of known cases are of Portuguese origin, this is not obligatory. The next research endeavour should be a search for the chromosomal site of the gene, using molecular biology technology such as those for recombinant DNA.

RÉSUMÉ: Nous avons examiné 138 cas d'une maladie décrite préalablement chez des sujets d'origine portugaise et qui a reçu plusieurs noms. Une analyse sur ordinateur de 46 items différents d'un examen neurologique uniformisé fait sur chaque patient nous a permis de délimiter les principales composantes du tableau clinique, de conclure que la grande variabilité d'expression ne contredit pas l'homogénéité de la maladie et de décrire l'histoire naturelle de cette entité que l'on devrait appeler ***"La Maladie de Machado-Joseph"***.

Cette maladie héréditaire se transmet de façon autosomale dominante et se présente comme une ataxie progressive avec ophtalmoplégie externe. Elle devrait être incluse parmi les ***"Dégénérescences multisystémiques ataxiques"***. Lorsque la maladie débute avant l'âge de 20 ans, elle peut se présenter sous la forme d'une importante spasticité, non progressive, mais souvent si sévère qu'elle peut s'accompagner du phénomène de "Gegenhalten" et de postures dystoniques sans dystonie franche. Il existe peu, dans cette entité, de symptômes que l'on peut qualifier d'extrapyramidaux, sauf pour l'akinésie. Par contre, lorsque la maladie débute après l'âge de 50 ans, le tableau clinique est surtout celui d'une polyneuropathie amyotrophique avec fasciculations associées à l'ataxie. Pour tous les autres cas, le tableau est le résultat d'un continuum entre ces deux phénotypes extrêmes, dont le déterminant principal est l'âge de début et le facteur secondaire, le lieu d'origine de la famille sous étude. Les composantes ataxiques et amyotrophiques de la maladie sont nettement progressives, à l'encontre de la composante spastique. Même si la majorité des cas connus sont d'origine portugaise, cette appartenance ethnique n'est pas obligatoire. Les recherches futures devraient se concentrer sur l'identification du site chromosomique du gène de la maladie, à l'aide des nouvelles technologies de biologie moléculaire.

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A. Historical Review

The first report of the entity we will analyze was made in 1972 by Nakano and collaborators (1972) from Boston, who studied 51 affected members of a family descending from one William Machado, a native of Bretanha on the Island of São Miguel in the Portuguese Azores, and whose children emigrated to Massachusetts in the late nineteenth and early twentieth century. The authors described the hereditary ataxic signs and stated that the syndrome, which appeared to be transmitted in an autosomal dominant fashion, also included nystagmus on lateral

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gaze, mild dysarthria, depressed or absent tendon reflexes, equivocal plantar responses, distal muscle atrophy and, in some patients, contraction fasciculations. A distal blunting of vibratory and position sense was also noted. It is of interest that in the patients examined by the authors, the ataxia of gait was said to appear late in life and to be slowly progressive. The disease, they said, did not correspond to olivo-ponto-cerebellar atrophy nor to the ataxic variations of familial spastic paraplegia. They therefore named it ***Machado disease***, implying the description of a new entity (Nakano et al., 1972).

The same year Woods and Schaumburg (1972) also described what they thought was a new disorder which they termed "nigro-spinodentatal degeneration with nuclear ophthalmoplegia". Again this family (the "Thomas" family) was of Portuguese origin and had migrated to Massachusetts where 12 cases were examined, one at post-mortem. In the typical picture as reported by these authors there is gait ataxia, nystagmus, extrapyramidal rigidity, and hyperreflexia. Spasticity and extensor plantars were more variable findings while mild weakness and distal muscular atrophy were present in more advanced cases. In contrast to the first paper, the authors noted that posterior column sensation had remained intact. The disease, as seen by Woods and Schaumburg (1972) has more features of spastic ataxia than the Machado form. In a subsequent chapter for the Handbook of Clinical Neurology (Woods and Schaumburg, 1975), the same authors confirmed and expanded their findings. They also described a second post-mortem case and listed the main physical findings in 11 family members they examined, emphasing the gait ataxia (10/11 cases), spasticity (3/11), hyperreflexia (9/11), and extrapyramidal rigidity (7/11).

A few years later, Rosenberg et al. (1976) independently described an autosomal dominant disorder in a family of Portuguese ancestry living in California, whose illness begins in the second, third or fourth decade, progresses for about 15 years with parkinsonian rigidity, spasticity, spastic dysarthria and abnormalities of eye movements. Facial fasciculations, facial myokymia and lingual fasciculations without atrophy were common and early manifestations. The authors state that the spasticity is the main problem responsible for the gait imbalance, speech difficulty, and dysphagia. Their patients had some rigidity, dystonia or athetosis, but these features were not prominent. Based on the neuropathological examination of one case demonstrating severe neuronal loss and astrocytic gliosis of the corpus striatum and substantia nigra, and a moderate neuronal loss in the dentate nucleus and red nucleus, the authors conclude to a new form of striatonigral degeneration. Although they cite the previous authors, they state categorically that this entity is distinct from nigro-spino-dentatal degeneration, olivo-ponto-cerebellar degeneration, dystonia musculorum deformans, Machado disease and Huntington's disease. The original ancestor of this California family was António José (Joseph) Bastiana, hence the name proposed: ***Joseph disease***. Shortly thereafter, Nielsen (1977) challenged the pathological conclusions, particularly the caudate and putamen involvment, and stressed the similarities with the report of Woods and Schaumburg (1972).

In 1976, Portuguese neurologists, aware of the previous descriptions, travelled to the Azores and identified 40 cases of a similar disorder (in 15 families) which was called "Doença da Ponta Ruiva" from a village on the Island of Flores (Coutinho et al., 1977). This preliminary report was followed by a more complete description of these cases (Coutinho and Andrade, 1978) in which the authors argue for a system degeneration involving cerebellar, pyramidal, extrapyramidal and spinal cord motor functions. They also give a thorough description of the clinical features as seen in all cases including the "Freitas" family from the Island of Flores. For the first time three separate but interrelated subtypes of the disease are identified: Type I, in which pyramidal and extrapyramidal abnormalities predominate; Type II with mainly cerebellar deficits and Type III with mainly distal muscle atrophy. In all types cerebellar signs and PEO are present. The authors conclude to a continuum of clinical expression in this dominantly inherited neurologic disease.

Meanwhile in Boston, Romanul et al. (1977) studied another Portuguese family from the Azores who suffered a progressive neurologic disease characterized by gait ataxia, features similar to Parkinson's disease in some patients, limitation of eye movements, widespread fasciculations of muscles, loss of reflexes in the lower limbs, followed by nystagmus, mild cerebellar tremor and extensor plantar responses. Two post-mortem studies were carried out. The presence of considerable variability in the clinical expression of the disease in individual members of their family, led the authors to conclude that this kinship had the same disease as those previously reported and that they represented a single genetic entity with variable expression. For the first time Machado disease and Joseph disease were united in what the authors proposed to call the ***"Azorean disease of the nervous system"***.

This report prompted a number of exchanges and field trips to the Azores (Dawson, 1977; Rosenberg, 1977a; Fowler et al., 1977; Romanul, 1977) which again confirmed the existence of similar cases on the Islands. Initially Rosenberg (1977) maintained that the type III cases were a different entity while Romanul (1977) was for "lumping", but objected to the term striatonigral degeneration. However, in his subsequent report on his 1977 field trip to the Azores, Rosenberg (Rosenberg et al., 1978) stated "it seemed likely that all reported families of similar ancestry represented a single genetic entity with variable expression". Rosenberg used the term "Joseph disease" to describe all cases he examined which, may cause ambiguity since it was first used to describe one type of the illness and was not the initial description of the entity. The Freitas family originally described by Coutinho and Andrade (1978) is now called the Sousa family, from the name of the earliest known ancestor. Rosenberg et al. (1978) also state that on the Island of Flores, they did not encounter a single example of type III, or the Machado form, with evidence of peripheral neuropathy, distal atrophy, and cerebellar findings. [In subsequent field trips, the present authors as well as Coutinho were able to observe at least 6 cases (nos 3, 6, 10, 16, 76, and 98 in our files) of this type on the Island of Flores].

Rosenberg and his group then launched the search for a molecular marker of "Joseph disease" (Rosenberg et al., 1979; 1981; Morrison and Rosenberg, 1983). Using two-dimensional acrylamide gels they examined proteins from skin fibroblast cultures and brain homogenates. They reported increases in certain proteins (possibly representing gliosis) in the putamen and cerebellum. They subsequently reported that the same proteins were increased in the brains of Huntington's disease patients and proposed a common primary deficit of glial-neuronal interaction in these disorders.

Meanwhile, Lima and Coutinho (1980) had discovered and described a new family residing in the village of Freixo-de-

Espada-à-Cinta, in northern Portugal, with no known relationship to the Azores or North America. Because this makes the term "Azorean disease" obsolete and incorrect, the authors propose the use of the eponym ***"Machado-Joseph disease"***, since the Machado family was the first to be described and the Joseph represent the largest and most comprehensively described family. The authors also propose some definite criteria for the disease:

"(1) An autosomal dominant mode on inheritance.

(2) Major neurologic picture including cerebellar ataxia and pyramidal signs (Type II), associated in variable degree with a dystonic-rigid extrapyramidal syndrome (Type I) or peripheral amyotrophy (Type III).

(3) Minor, but more specific, clinical signs such as progressive external ophthalmoplegia (PEO), dystonia, intention facial and lingual fasciculation-like movements, and bulging eyes."

This last feature had been recognized in the 1976 and 1977 field trips to the Azores. These clinical criteria have been accepted by Rosenberg and Fowler in their 1981 review, which summarizes the First International Symposium on this disorder held in June 1980 in Lisboa. The genetic aspects of the disorder were also reviewed by Sequeiros and Coutinho (1981), while Sachdev et al. (1982) concluded, from the neuropathological study of two patients from different families, that the disease represents a single entity. It should be noted that in both these cases, the neostriatum appeared normal. Finally Dawson et al. (1982) have studied electro-oculographic recordings in 26 patients with Machado-Joseph disease. All patients with clinically apparent disease had abnormal eye movements, with abnormal calorics, sinusoidal tracking, opticokinetic nystagmus, refixation saccades and gaze paretic nystagmus in that order of frequency.

The interest in this strange disorder in patients of Portuguese descent has prompted reevaluation of the presence of similar clinical complexes in non-Portuguese families. The first such kindred, American black in origin, was reported from Harlem Hospital in New York by Healton et al. (1980). The patients from this kindred have mostly the Type II phenotype. Sakai et al. (1983) also recently reported 4 cases from a non-Portuguese Japanese family, with neuropathologic confirmation in one case (degeneration of the substantia nigra, dentate nuclei, Clarke column and anterior horn cells of the spinal cord). There were two clinical types in the family. One was characterized by pyramidal and cerebellar signs with or without extrapyramidal signs; the other by cerebellar signs, loss of tendon reflexes, and peripheral sensory loss. Again there was autosomal-dominant inheritance. A second black family originating in the West Indies and living in California was recently described (Cooper et al., 1983) as well as a family from France originating from near the Spanish border and presenting with marked peripheral signs (Chazot et al., 1983). A brain scan in two patients showed cerebellar atrophy. A similar clinical presentation was described by Goto et al. (1982) in a Japanese family, but the pathological examination showed a dentato-rubro-pallido-luysian degeneration.

B. Unanswered Questions

As is obvious from the above historical review, there is still a considerable degree of uncertainty concerning many aspects of the disorder called Machado-Joseph disease. The unanswered questions are listed in Table 1.

Table 1: Machado-Joseph Disease

UNANSWERED QUESTIONS
1. ARE the various phenotypes indications of **genetic heterogeneity** or of a **continuum** of clinical expressivity in the same disease?
2. WHAT is the **typical** clinical **presentation** of the disease if it is a single entity?
3. WHAT are the modifyers of the clinical phenotype? What are the respective roles of sex, age of onset, sex of affected parent, genetic drift and place of origin?
4. IS the noted phenomenon of anticipation an observer bias?
5. WHAT is the **natural** history of this disease?
6. WHAT is the nosological place of Machado-Joseph disease within degenerative disorders of the CNS?

In the last two years the two senior authors had the opportunity to personally study 138 cases of this disorder from various regions of the world. The present paper will summarize our experience and attempt to answer some of the above questions through analysis of the objective neurological examination results.

Subjects and Methods

In 1979, the senior author was asked to examine a patient from South Africa who presented with the symptom complex previously described by Nakano et al. (1972) and by Rosenberg et al. (1976). It turned out that the patient was born in Lisboa and was a member of a second, previously unreported, mainland Portuguese family with Machado-Joseh disease. Subsequently we were able to examine three Canadians of Azorean origin with the same disease. This was the trigger to our interest in this disorder. In May 1982, thanks to the kindness of the neurological team from the University of Coimbra (Professor A.N. de Vincente) under the direction of Professor L. Cunha, we travelled to Terceira, São Miguel and Flores in the Portuguese Azores where we examined a total of 43 cases of Machado-Joseph disease including the large Sousa-Freitas family.

Shortly afterwards, a further 11 cases (including cases reported by Lima and Coutinho, 1980) were examined in Coimbra and the region of Freixo-de-Espada-à-Cinta in northeastern Portugal, near the border of Spain and two cases were seen in Lyon, France with Dr. G. Chazot. In the fall of 1982, both of us attended "Joseph Disease" Clinics in Los Angeles, and the San Jose area of the San Francisco Bay in California. This was made possible through the courtesy of Dr. Roger Rosenberg and of Mrs. Rose Marie Silva of the Joseph Diseases Foundation, Inc.. At these clinics a total of 40 cases (mostly from the Joseph family) were personally examined. Finally, 38 further cases were examined in the spring of 1983 at similar clinics of the Joseph Diseases Foundation in the Fall River area of Massachusetts again through the courtesy of Drs. R. Rosenberg and D.M. Dawson and of Mrs. Silva. The latter cases included patients from the families reported by Nakano et al. (1972), Woods and Schaumburg (1972), and Romanul et al. (1977).

The protocol followed for each of the 138 cases seen in the course of this study was always the same. After a clinical and genetic questionnaire to identify the individual within the large

pedigrees available and establish his age of onset and personal data, each patient was carefully examined following a strict protocol developped for ataxia by Pourcher and Barbeau (1980). In this protocol 48 items are objectively calibrated on a scale of 0 to 3: *0* is normal; *1*: mild; *2*: moderate; *3*: severe disability or deviation from normal. These items are grouped into 6 categories: cranial nerves (max. score 18); incoordination (42); tone (18); reflexes (24); peripheral signs (24); muscle strength (12, distal; 12, proximal). For computer analysis (Vax 750 Computer) using the statistical package for the social sciences (SPSS) program of the University of Montreal, scores for the measurement of individual signs were utilized. In addition "symptom complex" scores were calculated for "Periphery" (P),"Incoordination" (C), and "Spasticity" (S): the ***"Periphery Score"*** (max. 45) included items 27 to 32 if negative (decrease in reflexes), items 35 to 37 (atrophy and fasciculations), 41 and 42 (vibration sense), and 43 to 48 (decrease muscle strength); the ***"Incoordination Score"*** (max. 42) included items 7 to 20 (gait, Romberg, finger to nose, heel to knee, adiadocokinesia, postural tremor, tapping and drawing a spiral with each hand); finally the ***"Spasticity Score"*** (max. 42) included items 21 to 24, if increased (tone), 27 to 34 (reflexes if increased, plantars), and 47, 48 (clonus). Each of these symptom-complex scores was normalized to 100%. For each patient a ***P/S Ratio*** was calculated from the scores for "Periphery" and "Spasticity". From the P, C and S scores for each patient a clinical phenotype was determined according to the following rules: the highest of the three scores determined the major axis, while the second highest determined the minor axis, i.e. the direction for subtyping (see Figs 1 and 2 and legends). For example if the scores were thus: C (52), P (35), S (12), the patient would be classified as phenotype II B. In this way a total of 6 phenotypes can be defined (with scores in order of magnitude): I A (SPC), I B (SCP), II A (CSP), II B (CPS), III A (PCS), and III B (PSC). The total spectrum is illustrated in Fig. 1.

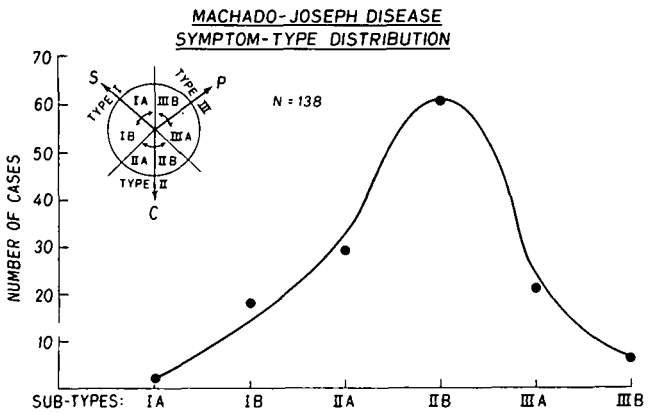

Figure 1 — Distribution of symptom types in 138 cases of Machado-Joseph disease. A subdivision of types is proposed using the major score as the main determinant axis and the minor score as the secondary directional factor for classification. S: relative spasticity score; C: relative incoordination score; P: relative peripheral score; all relative scores are expressed as per cent.

Results

In this section we will attempt to group the results in sections dealing with each of the major unanswered questions as listed in Table 1: however it is first important to characterize the total population to be studied:

A. The Target Population of Patients

There were 138 cases personnally examined by the two authors, 77 men and 61 women. As seen in Table 2, the average present age was 47 (range 10-80), while the average age of onset was 37 to 38 (range 1-73). Each of the individual "Symptom complex" scores: Spasticity (S), Incoordination (C) and Peripheral signs (P) are listed in the Table. It is obvious that for the majority of cases, incoordination is the prevailing abnormality, followed by peripheral symptoms and then by spasticity. Far behind is the ophthalmoplegia. This "average profile", as is evident from the range of scores, is subject to a wide variability, probably responsible for the controversy about heterogeneity.

Table 2: Machado-Joseph Disease — Description of Cases (mean ± SEM)

Variable	Total Group (N ± 138)	Men (N ± 77)	Women (N ± 61)	Range
Present Age	47.0 ± 1.3	47.2 ± 1.7	46.8 ± 2.1	10 - 80
Onset Age	37.8 ± 1.2	37.2 ± 1.6	38.6 ± 1.8	1 - 73
Duration of Illness	9.2 ± 0.6	10.1 ± 0.8	8.2 ± 1.0	0 - 34
Spasticity (S)	23.4 ± 2.0	24.5 ± 2.7	22.1 ± 2.8	0 - 100%
Knee-jerks	7.5 ± 0.4	7.2 ± 0.5	7.2 ± 0.6	1 - 13
Babinski	2.8 ± 0.2	3.0 ± 0.2	2.5 ± 0.3	0 - 6
Incoordination (C)	48.4 ± 2.1	50.0 ± 2.8	46.4 ± 3.3	0 - 95%
Periphery Signs (P)	34.6 ± 2.0	39.2 ± 2.6	28.7 ± 3.0	0 - 100%
Vibrations	4.3 ± 0.2	4.6 ± 0.2	4.0 ± 0.3	0 - 6
Atrophy	2.2 ± 0.2	2.8 ± 0.2	1.4 ± 0.2	0 - 6
Fasciculations	1.6 ± 0.1	2.0 ± 0.1	1.1 ± 0.2	0 - 6
Ophthalmoplegia (PEO)	1.8 ± 0.1	1.7 ± 0.1	1.8 ± 0.1	0 - 3

B. Genetic Heterogeneity Versus Continuum of Expressivity

As seen in the review of the literature, there are arguments on both sides of this controversy. Some authors claimed that the syndrome of spasticity, extrapyramidal and cerebellar signs typical of "Joseph disease" as seen in California is a separate genetic entity from the "Machado disease" observed in some parts of Massachusetts. Others, on the other hand, were convinced, from clinical and pathological data, that we are dealing with a continuum. When Coutinho and Andrade in 1978 reviewed 40 cases and described the three main phenotypes (see Introduction), they found that 47% of their patients presented with Phenotype III (mainly peripheral symptoms), 38% with Phenotype II (mainly incoordination) and only 15% with Phenotype I (mainly spasticity). In our much larger series of 138 cases (including most but not all of the previous 40), and using the same criteria and definitions, we now report a distribution of 20 - 65 - 15% respectively (Table 3). It must be remembered that Coutinho and Andrade's series does not include cases presently living in North America.

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Table 3: Machado-Joseph Disease — Phenotype Distribution

	Coutinho & Andrade (1978)*	Present Study (1984)
NUMBER OF CASES	40	138
PHENOTYPE I	15%	15%
PHENOTYPE II	38%	65%
PHENOTYPE III	47%	20%

* distribution of syndromes was: Ataxia 98%; Pyramidal signs 75%; Extrapyramidal signs 19%; Peripheral signs 63%.

Using only these three categories, it is impossible, in either case, to demonstrate a bimodal or multimodal distribution, even if it existed. Since a continuum of presentations was becoming probable, we tested this hypothesis by re-classifying our cases according to their primary and secondary scores in the three main divisions S, C and P. This gives a total of 6 possibilities, as seen in Fig. 1. It is evident that the distribution curve is typically Bell-shaped and not bimodal and this is confirmed by a heterogeneity chi-square analysis (Day, 1969). This argues in favour of a continuum of phenotypes, from the Spasticity type (I), through the Incoordination type (II), to the Peripheral type (III).

If this is the case, the distribution of individual symptom scores within the 6 sub-phenotypes should follow a series of intertwining sinusoidal curves. This is exactly the observed situation, as seen in Fig. 2. Thus we conclude strongly on the side of Machado-Joseph disease being a single entity and being manifested as a continuum of cardinal symptoms, as first postulated by Coutinho and Andrade (1978), and Rosenberg et al. (1978).

It should be emphasized that the pattern of inheritance in every family studied, in all regions, was always that of an autosomal dominant disorder. Numerous instances of father to son transmission were observed and, for all living cases we studied, except 6, an affected parent was known. In the 6 instances there were sufficient explanatory social circumstances to justify the lack of knowledge about the exact affected parent. Unfortunately a common origin, or genetic link, between all the reported families and those we examined is not yet available. This would be the best argument for the homogeneity and uniqueness of the syndrome.

C. "Typical" Clinical Presentation

Experience has long taught us that, in neurology, there is no such thing as a "typical" presentation for a given disease. However we can presume that any profile fitting a real majority of cases, would be as close as possible to such a presentation. Since 65% of our 138 cases presented with the old phenotype II, or our sub-phenotypes II A and B, (90/138 cases), and since the other cases fall according to a Bell shaped distribution, it is permissible to regard the majority presentation as the most probable one, if not the "typical" one.

(a) The main symptom in these patients is ***incoordination***, particularly ataxia of gait. This may constitute a surprise since the literature previously emphasized spasticity on one side, and peripheral signs on the other. Of the 138 cases examined by us, only 8 had incoordination relative (or "normalized") scores below 10%. In 6 of these patients the disease was in its first year

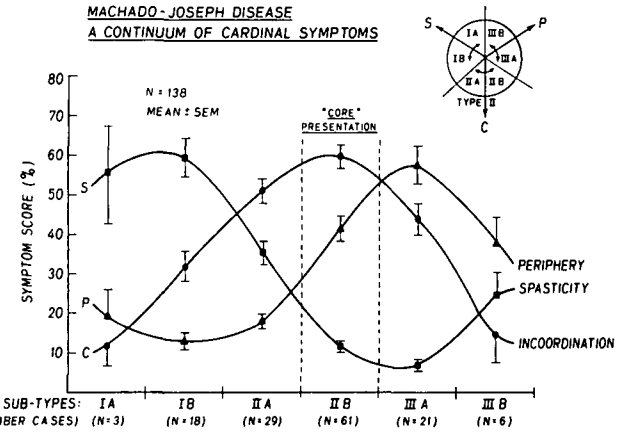

Figure 2 — Intertwining sinusoidal curves illustrating a continuum for each of the major symptoms characterizing Machado-Joseph disease. Phenotypes and symptoms as described in Fig. 1.

of evolution, while in the other two (14 and 15 years of evolution) the spasticity was such (100%, 90% spasticity relative scores) that any ataxia present was almost totally masked (0% and 9% respectively). Thus incoordination can be said to be a constant symptom in this disease, which therefore should be understood mainly as a hereditary ataxia (see below for discussion). Early, lurching, unsteadiness of gait was frequently reported in the first publications and has always been a feature of later reported cases. In addition to the gait disorder, more advanced patients also have incoordination of hand movements, dysarthria and impairment of ocular movements as manifestation of the hereditary ataxia. The speech is usually slow and indistinct rather than saccadic and explosive.

(b) The ***secondary symptom complex*** in the core patients (90/138 cases) varies according to the phenotypic sub-types A or B. In sub-group II A (29 cases), the relative scores are 35% for S and 18% for P, while in the more numerous sub-group II B (61 cases), the relative scores are P, 41%, and S, 13%. Most cases are thus closer to the "Machado" description than to the "Joseph" tableau. As will be seen later, however, the predominance of a given secondary feature varies with time and the evolution of the disease. A number of other symptoms characterize Machado-Joseph disease and it has been possible to analyze them in the course of our study:

(c) ***Spasticity:*** normal or increased knee-jerks are the norm in most cases. Diminished or absent tendon reflexes only appear very late in the disease after many years of evolution, or if the onset is after the age of 50. Even in phenotypic sub-groups III A and III B, where there can be severe amyotrophy, knee-jerks can be present or even increased. Finally, it should be noted that even in pure type III, equivocal or clear Babinski signs can be present. Patellar and ankle clonus is common in these cases, as is a certain degree of stiffness in the arms. The generalized spasticity accompanied by pharyngeal weakness will often be reflected in a high degree of spastic dysphagia and swallowing difficulties, as well as in a spastic dysarthria.

(d) ***Fasciculations***, or action muscle contractions, are usually absent during the first few years of the disease, except when the onset is after the age of 50. The muscle fibrillations are most

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often observed in the peri-buccal, or sub-ocular regions, particularly after some efforts ("intention myoclonus"). They may take the form of facial myokymias in the chin region. It should be noted that similar muscle movements can be seen in various forms of OPCA. We have observed it almost constantly in the OPCA family of the Gaspé Peninsula which we have previously reported (Wastiaux et al., 1978). The severity of limb fasciculations, on the other hand, is proportional to the duration of the disease and usually increases with phenotype number (Pearson Coefficient R = 0.35). However, severe fasciculations can be seen in type I A, while they can be absent in type III B.

(e) ***Vibratory sense.*** This is one of the signs most poorly measured in man. It should always be calibrated in seconds at the same spot (preferably the maleolar area). In Machado-Joseph disease, there is a clear relationship to duration of the disease, the Pearson correlation Coefficient being +0.31 ($p < 0.001$). Thus involvement of the spinal dorsal columns is an almost constant accompaniment of the disease, but it occurs relatively late in its course.

(f) ***External ophthalmoplegia (P.E.O.).*** The vast majority of the patients (89.6%) have some degree of external ophthalmoplegia (P.E.O.), usually progressive, but the symptom is not obligatory at any given moment. In P.E.O. negative cases, the duration of disease averages as high as 7.6 years. The severity of the P.E.O. generally increases with duration of the illness, in a statistically significant manner (Table 10). It is still possible, if rare, to have no P.E.O. after more than 15 years of evolution. P.E.O. typically begins with upward gaze limitation. The nystagmus can be horizontal and/or vertical and is accompanied by loss of saccadic eye movements. One often encounters early impairment of vertical gaze. As noted elsewhere, the eyes can be prominent with some eyelid retraction and this near-exophthalmia is marked by conjunctival venous congestion which is almost diagnostic. We have found diplopia to distant gaze to be one of the most constant and early symptoms, but it is rarely complained-of spontaneously by the patients and must be searched for.

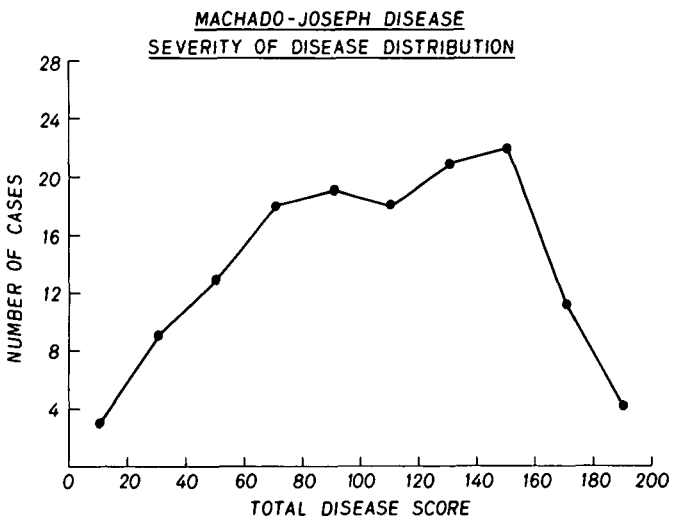

Figure 3 — Distribution of the 138 cases of Machado-Joseph disease according to severity of the disease expressed as a total disease score of the raw data (not of the relative symptom-complex scores).

Table 4: Machado-Joseph Disease — Severity of Signs (Total N = 138)

Variable	Direction of Change	Change: 0 Normal	1 Slight	2 Moderate	3 Severe
	+ Present − Absent	—		(No. of cases)	
A. SIGNS					
Ataxia	(+)	2	29	74	33
Babinski	(+)	25	55	25	33
Knee-jerks	(+)	21	19	23	29
	(−)	0	5	11	30
Atrophy	(+)	49	38	25	26
Vibrations	(−)	9	15	43	71
Fasciculations	(+)	45	25	19	49
P.E.O.	(+)	17	27	63	31
Weakness (Distal)	(+)	5	60	51	22
B. SYMPTOM COMPLEXES					
Incoordination	(+)	2	29	74	33
Spasticity	(+)	13	85	33	7
Periphery	(+)	2	69	57	10

(g) ***Amyotrophy*** is usually present after a few years of evolution. It can be observed in the distal muscle masses of the hands (interosseous), leg (peroneal) and feet and also just above the elbow and knee joints where a tell-tale dimple is often noted. Although amyotrophy is not a function of age of onset, it is however clearly related to duration of the illness ($r = 0.32$, $p<0.001$). With time it can become generalized and is usually accompanied by fasciculations.

(h) ***Muscle weakness.*** This symptom is eventually present in all cases particularly when there is amyotrophy. It is interesting to note that in very early onset cases (below age 15), the muscle weakness is definitely proximal and involves the shoulder and hip girdles. On the contrary, in late evolving cases, the muscle weakness is clearly distal. However, in these patients, except in the final stages, the muscle weakness is never very severe, and much less than in Freidreich's ataxia after the same number of years.

(i) ***Pes cavus*** and ***kyphoscoliosis*** are not prominent features of this form of hereditary ataxia, but they may occasionally be found, particularly when spasticity is marked.

(j) ***Intellect.*** In virtually all cases studied the intellect was totally intact. The few exceptions were always explained by concommittent damage to the CNS (at birth or following a cerebro-vascular accident).

It is of interest to note that the 138 cases we studied represented a normal distribution of disease severity. This is illustrated by the bell-shaped curve in Fig. 3 and by the actual distribution classification of Table 4. It is thus seen that for incoordination, the majority of cases (74) are classified as of "moderate" severity, whereas for both spasticity (S) and periphery (P) scores, the majority of cases (85 and 69 respectively) are said to be "slight" (Fig. 4). This confirms the above statements about the core, or "typical", presentation being predominantly a hereditary ataxia with two almost mutually exclusive directions for the secondary feature: towards spasticity or towards peripheral involvement.

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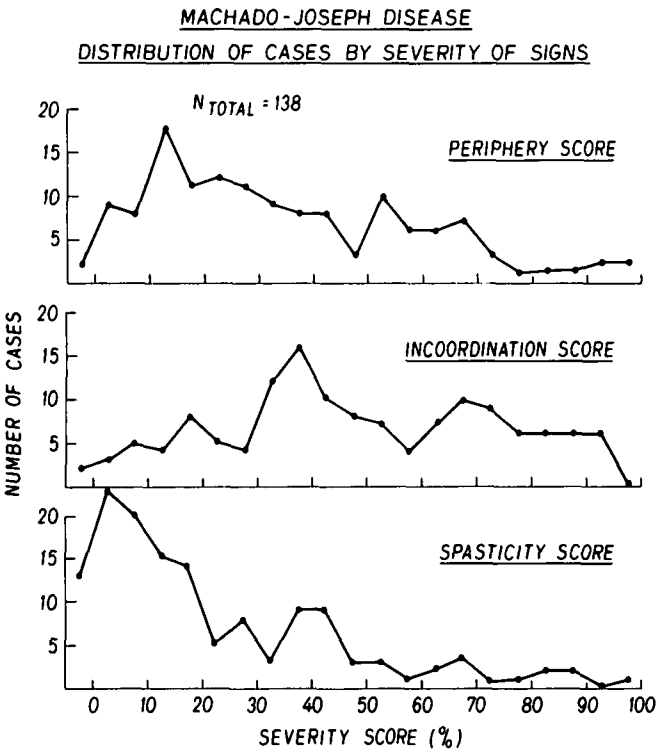

Figure 4 — Distribution of the 138 cases according to the severity of the individual cardinal sign relative scores.

Table 5: Machado-Joseph Disease — Affected Parent Transmission* (Total 138 cases)

	Father Affected	Mother Affected
No. of Cases	72	62
Age of Onset	38.5 ± 2.1	35.6 ± 2.2
Spasticity Score	19.9 ± 2.7	24.2 ± 3.6
Periphery Score	36.8 ± 3.4	33.3 ± 3.7
P/S Index	1.85	1.38
Incoordination Score	50.2 ± 2.3	45.6 ± 3.1

* 6: affected parents unknown
2: both parents affected

D. Clinical Phenotype Modifyers

It is evident from the above noted observations that the resulting clinical presentation in this disease is eminently variable, as it tends to be in most forms of hereditary ataxias (Schut, 1950; Schut and Böök, 1963; Schut and Haymaker, 1951), particularly of the autosomal dominant type. Many factors have been studied over the years to explain this kind of variability: sex, age of onset, sex of affected parent, influence of sibship rank and size, genetic drift and place of origin being the most important. We have studied each of the above factors in our 138 cases as they may influence the clinical presentation of individual patients.

(a) ***Sex:*** As seen in Table 2, the sex of the patient does not appear to play any significant role in the clinical picture. The only difference which approaches, but does not reach, statistical significance is the slightly higher prevalence of peripheral symptoms in men. This is true for the combined complex score and also a positive trend for the individual components of vibratory sense, peripheral muscle atrophy and the presence of fasciculations. In this respect, it is of interest to recall that amyotrophic lateral sclerosis, and in general the presence of fasciculations, tend to be more frequent in males.

(b) ***Sex of affected parent:*** In another autosomal dominant neurological disorder, Huntington's chorea, a peculiar phenomenon has been noted (Barbeau, 1970): when the onset is below the age of 20, and more so before the age of 10, the disease is inherited mainly from the father. Various explanations have been proposed, still unsatisfactorily, to this observation. The most intriguing one (Myers et al., 1982) is probably the postulated presence of a maternal factor. We studied this problem in our cases of Machado-Joseph disease. As can be seen in Table 5, 72 patients inherited the disease from their father and 62 from their mother (N.S. difference). In 6 cases the affected parent was unknown and in 2, both parents were affected. There is no significant difference between the two groups as regards age of onset, spasticity, periphery and incoordination scores, but one can note a trend towards a higher P/S index when the affected parent was male. This trend becomes more evident when the transmission is male to male as compared to female-female (Table 6). Thus in Machado-Joseph disease one does not find the phenomenon of earlier onset with paternal transmission reported in Huntington's chorea.

(c) ***Sibship rank order and size:*** For some diseases the order in which the child appears seems to influence some of the clinical characteristics (Andermann et al., 1976). In our own series of

Table 6: Machado-Joseph Disease — Transmission Types* (mean ± SEM)

	TYPES			N	Age Onset	Periphery	Spasticity	P/S Ratio
	Parent		Child					
(1)	Male	—	Male	34	36.8 ± 3.3	39.5 ± 4.6	22.3 ± 3.9	1.77
(2)	Male	—	Female	38	39.7 ± 2.5	30.8 ± 4.8	17.1 ± 3.9	1.81
(3)	Female	—	Male	39	34.3 ± 2.3	37.7 ± 4.4	25.4 ± 4.6	1.48
(4)	Female	—	Female	23	37.7 ± 4.6	28.8 ± 6.9	22.1 ± 6.1	1.31

* 6: affected parents unknown
2: both parents affected

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Table 7: Machado-Joseph Disease — Rank Order and Size of Sibships

A. SIZE OF SIBSHIPS (affected cases)	No. Sibships	B. RANK ORDER OF AFFECTED CASES	
		First child	23
		Second child	28
Only one case	84	Third child	31
Two cases	14	Fourth child	19
Three cases	6	Fifth child	20
Four cases	2	Above Fifth child	17

C. SIZE OF TOTAL SIBSHIPS	No. Sibships	No. cases
1 to 3 children	30	44
4 to 6 children	32	38
7 to 10 children	21	32
more than 10 children	13	24

Table 8: Machado-Joseph Disease — Sibship Clinical Type Distribution

(1) **NUMBER OF SIBSHIPS** (2 or more Sibs examined)	22
a) 2 sibs affected	14
b) 3 sibs affected	6
c) 4 sibs affected	2
(2) **NUMBER OF CASES IN THESE SIBSHIPS** (examined)	54
(3) **SPREAD OF CLINICAL TYPES** (max. 6 types)	Number of sibships
a) No Spread	5
b) Spread 1	12
c) Spread 2	4
d) Spread 3	1
e) Spread 4	0
f) Spread 5	0
(4) **SPREAD OF AGE OF ONSET** (Years)	5.2 ± 1.5

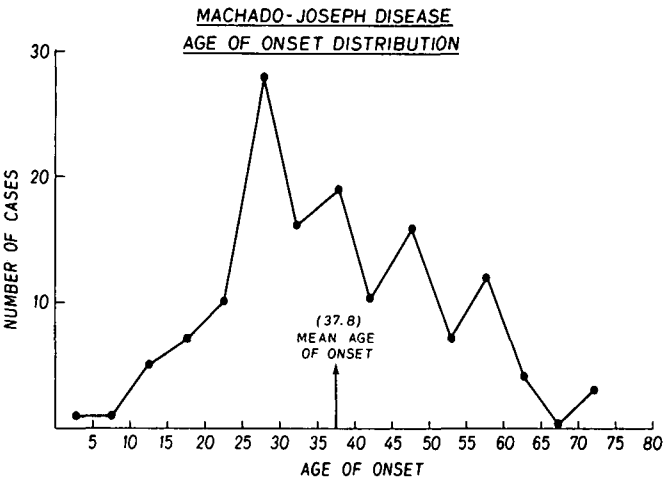

Figure 5 — Distribution of the age of onset in 138 cases of Machado-Joseph disease.

Table 9: Machado-Joseph Disease — Sex of Affected Parent By Age-of-Onset

Age-of-onset Cohort in affected children	N in cohort	Affected Parent	
		Father	Mother
10 - 15 yrs	5	1	4
20 - 25 yrs	14	7	7
30 - 35 yrs	25	15	10
40 - 45 yrs	17	10	7
50 - 55 yrs	15	10	5
60 - 65 yrs	7	7	3
TOTALS:	83	47	36

138 cases of Machado-Joseph disease there is no evidence of any influence of this factor (Table 7), nor is there any relationship between sibship size and prevalence of cases, except as predicted statistically for the summation of individual probabilities.

It is also important to note that there is a certain amount of homogeneity in symptoms and age of onset between affected sibs of the same sibship. As seen in Table 8, in 5 multicase sibships there is no spread between the clinical sub-phenotypes (maximum possible spread 5); in 12 sibships the spread is only one, in 4 sibships it is 2. Thus in 22 multi-case sibships, the maximum spread is equal or inferior to one sub-type in 17 instances. In only one instance is the spread greater than 2. Similarly the age of onset within these sibships is relatively constant.

(d) ***Age of onset:*** The age of onset curve for the whole group of 138 cases follows more or less the normal distribution (range from 1 to 73 years) (Fig. 5), with possibly some mild skewing of the curve towards a younger age. Although the average age of onset of the whole group is 37.8 years (Table 1), most cases indeed start between the ages of 21 and 30. The sex of the affected parent does not seem to have a major effect upon the age of onset, except the cohort with age of onset between 10 and 15 years where the affected parent is more often the mother (Table 9). Thereafter fathers appear to predominate, but never to any significant degree in the cohorts examined.

The age of onset appears, however, to exert a very significant effect upon the clinical presentation of the patients. In Fig. 6 we see the evolution of symptom complexes for the whole group of 138 cases according to the age of onset of the disease. There are two patients with onset below the age of 10. In both cases, there is evidence that both parents may have been affected. The clinical presentation in these youngsters was dominated by marked muscle atrophy, mainly of the proximal muscle groups in the shoulder and hip girdles.

When the age of onset is between 10 and approximately 30, the main symptom is spasticity, either alone or with significant incoordination. After the age of onset of 30, the evolution of the symptom-complex scores will significantly diverge. Spasticity is found with decreasing frequency while incoordination and peripheral signs significantly increase with age of onset. In all three instances the Pearson correlation coefficient between age of onset and the symptom-complex score is highly significant as indicated in Fig. 6 and Table 10. It can also be seen, that individual signs such as fasciculations and vibratory perception (positively) and knee-jerks (negatively) are also correlated with age of onset.

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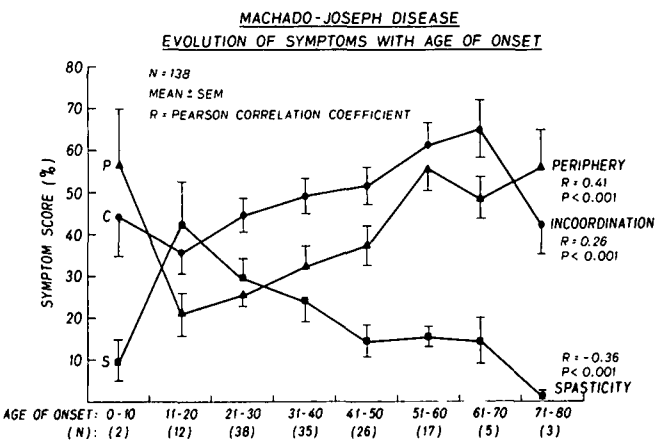

Figure 6 — Evolution of the three cardinal symptoms in Machado-Joseph disease according to the age of onset in 138 cases.

Table 10: Machado-Joseph Disease — Statistical Correlations (Total N = 138)

	Correlations	Pearson r	Slope	p. Value
1. AGE OF ONSET	vs duration	0.0989	–	0.168
	coordination score	0.2633	+	< 0.001
	spasticity score	0.3612	–	< 0.001
	periphery score	0.4154	+	< 0.001
	fasciculations	0.3571	+	< 0.001
	vibrations	0.3136	+	< 0.001
	knee jerk	0.5451	–	< 0.001
	Babinski	0.0173	–	0.433
	atrophy	0.1745	+	0.241
2. DURATION	vs incoordination score	0.5639	+	< 0.001
	spasticity score	0.0613	+	0.137
	periphery score	0.4685	+	< 0.001
	fasciculations	0.3187	+	< 0.001
	vibrations	0.3749	+	< 0.001
	knee jerk	0.1767	+	0.042
	Babinski	0.2190	+	0.016
	atrophy	0.3236	+	< 0.001
	P.E.O.	0.3286	+	< 0.001
3. Incoordination score	vs spasticity score	0.1489	–	0.073
4. Incoordination score	vs periphery score	0.6002	+	< 0.001
5. Spasticity score	vs periphery score	0.2654	–	0.04

Thus, most of the variability observed between the many clinical phenotypes of Machado-Joseph disease can be attributed to the factor of age of onset. Except in the exceptional cases of possible homozygotes, an early onset will usually lead to a form of spastic ataxia ("Joseph" phenotype). A "normal" (20-40) age of onset will be manifested by a normoreflexic ataxic syndrome, while a later age of onset (> 40) will tend to emphasize peripheral deficits in nerve conduction, atrophy and fasciculations ("Machado" phenotype) along with severe ataxia. There are individual exceptions to this rule, of course, but a study of the group as a whole is highly significant in the above noted directions.

Table 11: Machado-Joseph Disease — Symptoms By Place of Birth — Symptoms Scores (%) mean ± SEM

Place of Birth	N (Total: 138)	Incoordination	Spasticity	Periphery
PORTUGAL	12	44.7 ± 8.5	39.2 ± 8.2	34.5 ± 7.0
FRANCE	2	69.0 ± 17.0	9.5 ± 7.5	60.0 ± 9.0
AZORES				
— Flores	23	52.4 ± 5.8	14.5 ± 2.9	40.3 ± 5.2
— Bretanha, SM.	14	45.0 ± 5.7	11.4 ± 2.6	32.7 ± 5.2
— S. Miguel	20	40.6 ± 5.9	31.6 ± 7.7	36.1 ± 5.2
— Other Isles	1	36.0	0.0	13.0
CALIFORNIA				
F2 — Flores	10	62.4 ± 4.5	23.3 ± 5.1	39.4 ± 5.6
F2 — Mass.	3	49.3 ± 12.8	23.7 ± 9.7	36.3 ± 8.9
F3 — Azores	21	51.1 ± 5.6	24.1 ± 4.6	31.6 ± 6.2
MASSACHUSETTS				
F2 — Flores	2	38.0 ± 0.0	44.0 ± 11.0	11.0 ± 0.0
F2 — Bretanha	1	67.0	43.0	29.0
F2 — S. Miguel	9	56.7 ± 9.8	18.0 ± 6.3	47.7 ± 6.7
F3 — Azores	20	40.9 ± 4.9	25.7 ± 5.1	23.4 ± 5.5

(e) ***Genetic drift and place of origin:*** From the original descriptions of "Machado disease" and of "Joseph disease", the divergences were so marked that it was first thought that different diseases were being reported. As further studies were carried out on large groups of patients in different parts of the world (California, Massachusetts, Azores, Portuguese mainland) it became evident that the various phenotypes tended to congregate in certain families and in certain regions. As the senior authors were able to study a large group of patients from all these regions (same examiners and same protocol), it is interesting to look at our specific results.

In Table 11 are given the scores for the principal symptom-complexes for all of the 138 patients listed according to their place of birth and, for North American born cases, according also to the place of origin of their families. Two extremes are seen: cases in mainland Portugal, and to a lesser extent California, are much more spastic than those in France. Conversely, peripheral signs are predominant in France, Flores and Massachussets born descendants from São Miguel. Other areas are somewhat middle ground between the two extremes. This diversity becomes more evident when the P/S ratio (ratio of Peripheral to Spastic signs) is considered. We have illustrated this in Fig. 7. It is seen that the P/S ratio is inferior to one (0.9) in mainland Portugal and remains about the same on the Island of São Miguel, except in the region of Bretanha where peripheral signs are more important (P/S ratio 2.9). This latter admixture is also found on the Island of Flores (P/S ratio 2.8) where most of the inhabitants originated from the other Azorean Islands. On the other hand patients born in the U.S.A. from Azorean immigrants obviously originated from different pools. In California the first native born generation (F-2) patients have a P/S ratio of 1.7, which in the F-3 generation becomes 1.3. In Massachussets the F-2 P/S ratio is 2.6 and it soon becomes 0.9 in the F3 generation.

These shifts in clinical presentation could be due to genetic drift or to the so-called anticipation phenomenon in the age of onset. We have further studied these factors (see infra).

It thus appears that what looks as different regional (U.S.A.) phenotypes is probably due to the fact that a given isolate

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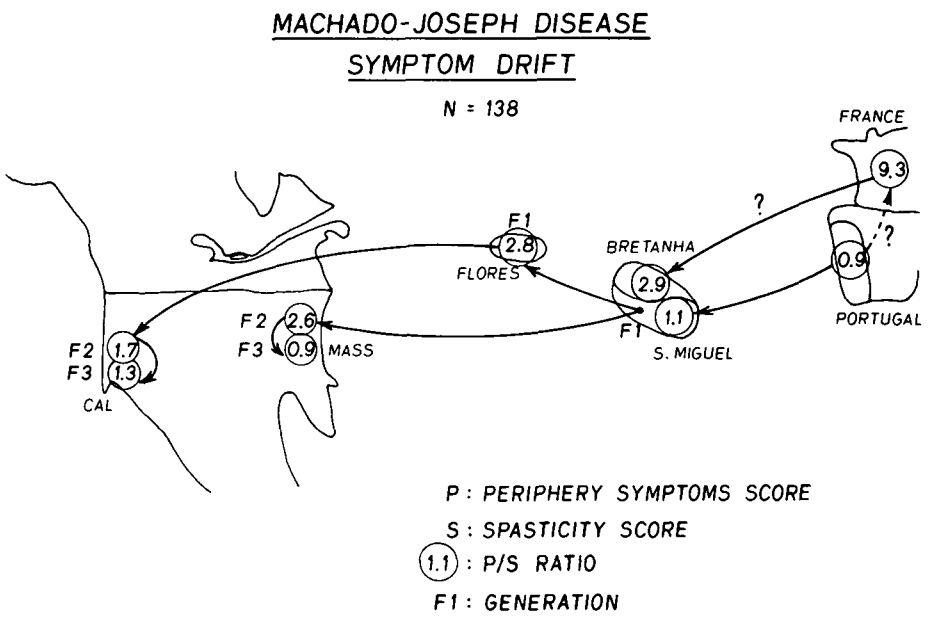

Figure 7 — Possible evolution of the main symptoms of Machado-Joseph disease in correlation with the geographic isolates and migrations. The P/S ratio represents the ratio of the relative scores for peripheral symptoms to those for spasticity. F1, F2, F3 represent successive generations.

Table 12: Machado-Joseph Disease — Description of Main Familial Units (mean ± SEM)

Variable	Kindred A	Kindred B	Kindred C	Kindred D	Kindred E	Kindred F
1. N. cases examined	11	9	16	5	5	5
2. Place of origin	Flores	Bretanha, S.M.	California	Portugal	Portugal	Flores
3. Ancestral name	**SOUSA**	**MACHADO**	**BASTIANA**	**POIARES**	**RATO**	**ESTACIO**
4. Age of onset	28.2 ± 2.4	38.5 ± 4.5	32.7 ± 2.5	33.8 ± 5.0	41.6 ± 8.1	32.8 ± 5.0
5. Duration	10.9 ± 3.5	10.6 ± 3.1	9.7 ± 1.8	16.0 ± 3.9	6.6 ± 2.7	6.4 ± 2.4
6. Incoordination score	56.3 ± 11.6	39.6 ± 6.6	53.2 ± 5.8	59.4 ± 12.9	23.8 ± 9.8	41.8 ± 12.7
7. Spasticity score	25.2 ± 6.3	17.1 ± 9.0	26.3 ± 3.9	55.2 ± 13.8	35.2 ± 9.5	18.0 ± 7.3
8. Periphery score	27.6 ± 6.6	31.2 ± 4.2	29.7 ± 5.7	44.8 ± 12.2	20.6 ± 9.7	26.2 ± 12.9
9. P/S Ratio	1.09	1.82	1.13	0.81	0.58	1.46
10. **SYMPTOM TYPE VARIATIONS WITHIN KINDREDS**						
Type I A	0	1	0	0	0	1
Type I B	1	0	2	2	2	0
Type II A	4	1	7	1	1	1
Type II B	5	5	6	1	0	3
Type III A	0	2	1	0	1	0
Type III B	1	0	0	1	1	0

derived its founder from one part of the mixed patient pool of the Azores, while another isolate inherited its founder from another part of that pool. In the Azores, many generations are known between the present patients and the immigrants from mainland Portugal, and perchance from elsewhere. It is also possible that a variety of inherited modifying factors may have entered that pool, ready to segregate again once the families are removed from that mixed milieu and particularly once they are "inoculated" into a virgin gene pool.

One possibility that should be considered is that the original gene has seen its onset modified to a later age by an inherited modifyer factor introduced independently into the Azores and subsequently gradually lost after a few generations in the U.S.A. Thus the present F3 generation cases would represent a return to the original gene expression.

This hypothesis could only be considered seriously if we could be sure to have eliminated the artefacts accounting for anticipation in the age of onset, artefacts that would favour more spastic forms since the cases are younger (see infra).

The findings summarized through a study of the evolution of P/S ratios, can somewhat be confirmed by the examination of individual families. As seen in Table 12, we were able to obtain 6 families where at least 5 members were examined by us. Again it is quite evident that there is homogeneity of presentation within a given family group. Thus the POIARES and RATO kindreds from mainland Portugal are uniformly more spastic than the ESTACIO kindred from Flores or the MACHADO kindred from São Miguel. The SOUSA kindred from Flores and the JOSEPH (BASTIANA) family from California are in between these two groups.

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Table 13: Machado-Joseph Disease — Modification of Symptoms in Parent-Child Comparisons, so-called "Anticipation" (mean ± SEM)

Generation	Number of Pairs	Age of Onset	Incoordination Score	Spasticity Score	Periphery Score	P/S Ratio
F1	14	48.3 ± 3.8	51.9 ± 9.1	13.2 ± 4.5	50.0 ± 8.4	3.79
F2	14	21.5 ± 3.5	31.0 ± 5.5	15.0 ± 4.3	24.9 ± 6.9	1.66

In conclusion, one can state that the clinical presentation, depending principally on the age of onset, will be clearly influenced by the gene pool and the area from which the patient originates. These traits will tend to hold true within a kindred, thus suggesting that the modifyer factors are genetically determined and possibly independently introduced into the gene pool. Sex of the patient, sex of the affected parent, sibship rank order and size do not appear to be significant factors in the clinical variability observed.

E. The Phenomenon of Anticipation

In many autosomal dominant disorders, including particularly the inherited ataxias, some authors have noted anticipation of the age of onset with succeeding generations. This has been the case also with Machado-Joseph disease (Coutinho and Andrade, 1978). Most geneticists immediately reject these claims as observation artefacts, but this explanation is usually hard to accept for the clinician. In reality, the artefact is due to the observation, at any given time, of two biased groups: the young patients starting their disease who are numerous and, in the older generation, the survival at that moment in time of only the fittest individuals, or of those whose onset was late, the early onset cases from earlier generations having by that time "run the course of their disease" and therefore disappeared. Since we had the opportunity to examine within two years a large cross section of this diseased population, we thought it would be worthwhile to verify this explanation, particularly since, as seen in Table 13, the so-called "anticipation phenomenon" was clearly observed in the 14 parent-child comparisons we could study. In fact the anticipation in these comparison pairs reached 26 years and was clearly translated into a phenotypic variation: The F1 generation being much more pheripheral and ataxic, with a P/S ratio of 3.79 compared to 1.66 in the F2 generation. This phenomenon could in great part be responsible for the geographic phenotypic drift noted in previous paragraphs and in Fig. 7. Finally, as seen in Table 14, this anticipation was not related to the sex of the affected parent, thus not secondary to a postulated maternal factor.

To look further into this effect we analyzed the surviving cohorts (by 5 year spans) for age of onset and observed duration (Table 15). It is quite evident that patients born between 1901 and 1925, and surviving to be examined, had a much later age of onset (53.4 years) than those surviving from the following two 25 years periods (age of onset: 33.8 and 19.3 years repectively). For the first two 25 years spans, the observed duration of illness did not vary (circa 10-13 years), indicating that in both groups the disease was running its usual course and that only the later onset cases were surviving to be examined. For the latest group (those born after 1951) the disease had only run for an average of 3.9 years.

This variation in age of onset between surviving cohorts is clearly translated into very different clinical profiles as seen in Table 16. Whereas the recent cohort (1951-1955) was mainly spastic (P/S ratio of 0.56), the oldest cohort (1916-1920) whose age of onset averaged nearly 53 years, was much more peripheric (P/S ratio of 3.97). This, in all points, confirms the hypothesis that the so-called anticipation phenomenon is an observation artefact because, at any given moment, the population available for study is not a random distribution of clinical phenotypes, but the result of a "weeding-out" process determined by the selective death of earlier onset cases who have run out the normal course of their illness. Again it must be repeated that the main determinant of clinical phenotype is the age of onset of the illness given a more or less finite course. The above noted "weeding-out" process is thus a secondary consequence of the factors at play in determining that age of onset in a given kindred or population. These factors, possibly also inherited, are still largely unknown, but extremely important for phenotype determination.

Table 14: Machado-Joseph Disease — Anticipation By Sex of the Affected Parent (mean ± SEM)

Affected Parent	Sample Size	Anticipation No. Years
Father	8	23.7 ± 3.4
Mother	6	23.3 ± 6.9

Table 15: Machado-Joseph Disease — Surviving Cohort Analysis of Age of Onset and Observed Duration of Illness

Age Group	N Total = 138	Observed Age of Onset	Observed Duration of Illness
1900 - 1905	4	60.0 ± 5.30	18.8 ± 4.69
1906 - 1910	3	70.0 ± 3.00	4.3 ± 2.96
1911 - 1915	6	59.8 ± 1.98	8.2 ± 2.65
1916 - 1920	14	53.2 ± 2.06	12.0 ± 1.97
1921 - 1925	12	41.9 ± 3.55	16.3 ± 3.74
First 25 years	(39)	53.48 ± 2.71 (24-73)	12.77 ± 2.11 (0-34)
1926 - 1930	12	43.7 ± 1.80	10.2 ± 1.99
1931 - 1935	15	36.1 ± 2.10	13.6 ± 1.96
1936 - 1940	18	34.1 ± 1.51	8.8 ± 1.50
1941 - 1945	15	31.7 ± 1.19	7.6 ± 1.46
1946 - 1950	16	27.9 ± 2.03	10.1 ± 3.10
Second 25 years	(76)	33.83 ± 2.03 (12-50)	10.00 ± 1.87 (0-32)
1951 - 1955	9	25.3 ± 1.62	3.3 ± 1.18
1956 - 1960	6	20.8 ± 0.75	4.0 ± 0.91
1961 - 1965	4	14.0 ± 1.0	3.5 ± 3.50
1966 - 1970	3	10.5 ± 3.50	3.5 ± 3.50
1971 - 1975	1	1.0	9.0
Third 25 years	(22)	19.35 ± 1.81 (1-30)	3.87 ± 1.31 (0-9)

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Table 16: Machado-Joseph Disease — Cohort Profile Analysis (mean ± SEM)

Symptoms	Recent Cohort (1951 - 1955)	Mid Cohort (1936 - 1940)	Late Cohort (1916 - 1920)
N	9	18	14
Present Age	28.57 ± 0.75	43.57 ± 0.27	63.90 ± 0.47
Age of Onset	25.29 ± 1.62	34.14 ± 1.51	52.72 ± 1.92
Duration of Illness	3.28 ± 1.18	9.43 ± 1.55	11.18 ± 1.96
Incoordination Score	20.0 ± 6.20	47.79 ± 6.78	63.27 ± 5.53
Spasticity Score	24.0 ± 7.31	31.64 ± 6.71	12.18 ± 3.34
Periphery Score	13.42 ± 2.89	33.79 ± 5.94	48.36 ± 6.87
Symptom Type	3.00 ± 0.65	3.71 ± 0.28	4.18 ± 0.12
P.E.O.	1.14 ± 0.25	2.21 ± 0.21	2.0 ± 0.35
Fasciculations	0.42 ± 0.19	1.93 ± 0.33	1.81 ± 0.37
Knee Jerk	10.29 ± 0.71	9.43 ± 0.98	4.81 ± 1.09
Vibrations	3.42 ± 0.52	3.64 ± 0.59	5.54 ± 0.20
Babinski	1.57 ± 0.29	3.14 ± 0.64	2.81 ± 0.74
Atrophy	0.85 ± 0.45	3.21 ± 0.61	2.81 ± 0.68
P/S Ratio	0.56	1.07	3.97

F. The Natural History of the Disease

The "cross-section in time" approach which we have utilized for the present inquiry is not the best way to study the natural history of an illness, but it is the quickest if a sufficiently large sample of cases is available, as in our investigation. Our approximations, however, will eventually have to be confronted to actual observations over long periods of time.

(a) ***Phenotypic variations with time:*** As noted previously, three main phenotypic presentations have been described, and used, since 1978. Because of good records made available to us from previous investigations of these cases, we have been able to follow the variations over time in 28 cases studied at least 5 years apart. In Table 17, we can see that 4 cases went from Phenotype I to Phenotype II, 2 from Phenotype I to Phenotype III and 2 more from Phenotype II to Phenotype III. The reversed evolution (III to II or to I) was never observed. In the other cases no evident phenotypic change occured. This small sample clearly indicates that a clinical phenotype is not fixed and can change with time. It is thus not the equivalent of a genotype ("heterogeneity"), but is the result of the interaction of many evolutive factors. One of the most important factors is undoubtedly the age of onset. As can be seen in Table 18, the average age of onset is higher for Phenotype III than for Phenotype I, but the ranges within each phenotype are quite wide, and often overlap.

(b) ***Duration of illness:*** In the present cross section, the average duration of illness in living examined cases was 9.2 ± 0.6 years (Table 2), with a range 0 to 34 years. The longest observed durations are not necessarily in patients with younger age of onset, but they usually correspond to patients with a major peripheral component to their clinical picture.

Retrospective accurate histories could be obtained from only 17 patients who had died and in whom an age of onset could be reasonably established. In these patients the average duration of symptoms (usually of ataxia) was 15.6 years. It is, of course, much more difficult to establish the duration of symptoms and signs, such as fasciculations and nerve conduction defects, of which the patients themselves are not aware. It is not impossible that certain signs were probably present much earlier than suspected. Only a prospective investigation of young siblings and children of known cases will help clarify this point.

Table 17: Machado-Joseph Disease — Clinical Phenotype Modification With Time (N = 28 cases with examinations more than 5 years apart)

	INITIAL PHENOTYPE		LATER PHENOTYPE	OBSERVED NO.
1.	PHENOTYPE I	→	PHENOTYPE II	4
2.	PHENOTYPE I	→	PHENOTYPE III	2
3.	PHENOTYPE II	→	PHENOTYPE III	2
4.	PHENOTYPE II	→	PHENOTYPE I	0
5.	PHENOTYPE III	→	PHENOTYPE II	0
6.	PHENOTYPE III	→	PHENOTYPE I	0
7.	NO CHANGE IN PHENOTYPE OVER 5 YEARS			20

Table 18: Machado-Joseph Disease — Age of onset of various Phenotypes

SUB-PHENOTYPES	N	$\bar{X}$ AGE OF ONSET	RANGE
I A	3	27.0	25 - 28
I B	18	26.2	13 - 52
II A	29	32.6	18 - 54
II B	61	40.7	14 - 64
III A	21	46.5	1 - 73
III B	6	35.2	12 - 53

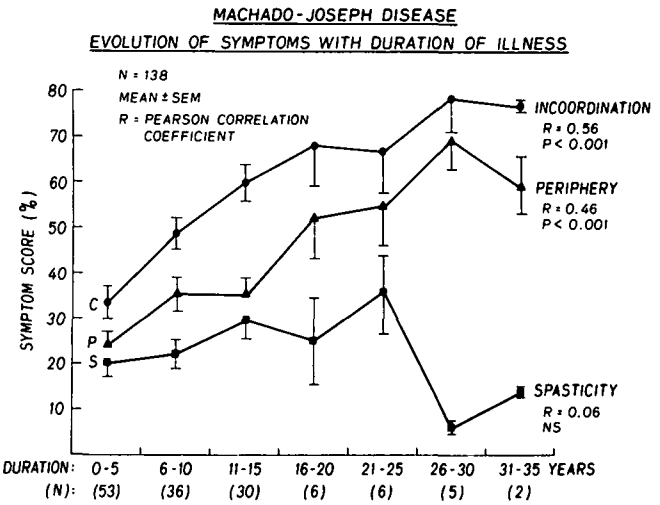

Figure 8 — Evolution of the three cardinal symptoms of Machado-Joseph disease with duration of the illness.

(c) ***Evolution of symptoms:*** Because of our large number of cases, we have been able to establish a cross-section of the clinical profile at each 5 year-duration interval of the illness, independently of the age of onset. Fig. 8 illustrates these findings. It is seen that the symptom-complex of Spasticity (S) which includes muscle tone, knee-jerks, clonus, Babinski signs, is present from the first year of diagnosis and does not essentially change even after 25 years of evolution (Pearson correlation coefficient of r = 0.06, NS). In later years the existing spasticity is less evident because of the progressive neuropathy which reduces the knee-jerk. On the other hand, it is quite clear that both incoordination and peripheral signs are progressive in uninterrupted fashion (Pearson correlation coefficients of r = 0.56

and 0.46, both highly significant). It can thus be stated that Machado-Joseph disease is a progressive inherited ataxia coupled to a progressive mixed neuropathy with atrophy and fasciculations.

It is more difficult to study the evolution of the secondary symptoms and signs in this disease because they are not always observed or reported. It can, however, be stated that the external ophthalmoplegia is also clearly progressive in nature. There is a positive correlation ($r = 0.329$; $\rho<0.001$) with duration of the illness as noted in our patients (Table 10).Nystagmus, when present, does not appear to be progressive, although there may be some progression to the loss of saccadic eye movements. There is clearly some progression to the exophthalmia occasionally noted at random within these families. Studies such as those carried out by Dawson and collaborators (1982) will eventually permit clearer answers to these questions.

Many authors (see introduction) have claimed the presence of extrapyramidal rigidity in some of these patients. We must state that in our study of 138 cases, many of whom had previously been reported, the two senior authors have never seen what we would unequivocally call "extrapyramidal rigidity". We saw some patients with an almost total immobility which was due always to a combination of spastic contractures and some akinesia of facial expression. Cogwheeling was not present in any of the patients we examined. In very advanced cases the classical countermovements of "Gegenhalten" were definitely present.

The combination of severe contractures and akinesia with postural abnormalities has also led some authors to talk about severe extrapyramidal dystonia in many of these patients, particularly towards the end of the natural course of the illness or in early onset cases. In our opinion this is due to a confusion of terms. "Dystonia", an extrapyramidal sign characterized by sustained abnormal movements and changes in tone, must be distinguished from "dystonic postures". The latter can be seen in a variety of entities which have nothing to do with the extrapyramidal system, and are particularly frequent in advanced cases of ataxia, particularly in severe Friedreich's disease, where a major loss of position sense is present. The previously mentioned "Gegenhalten" phenomenon and spastic extension spasms observed in these patients probably contributed to the confusion. We did indeed observe these so-called "dystonic postures" in many advanced cases of Machado-Joseph disease, involving the face, head, neck and limbs, particularly when muscle weakness or position sense loss were also noted and most often in reaction to an unrelated motor act, like walking. These postures are very similar to what is seen in infantile encephalopathies and at best, could be considered as secondary dystonia-like manifestions, but they are not primarily extrapyramidal in nature. These postures are present mainly in very advanced cases, even if young. The only evident consequence of the loss of cells in the substantia nigra in some of these patients is akinesia (loss of motor initiation, loss in the ability to change from one motor pattern to the next and increased fatiguability). It should also be mentionned that bizarre posturing of the fingers, and limbs in "unnatural positions", were also noted in the Schut family of OPCA (Schut and Haymaker, 1951) and in many other inherited ataxia kindreds.

(d) ***Other neurological entities seen in the Azores:*** It is important to place the presence of Machado-Joseph disease within the Portuguese population of the Azores in proper perspective. This is not the only inherited neurological disorder present or reported from these islands. During our 1982 field trip to Flores, Terceira and São Miguel we were able to examine a number of cases of hereditary, recessive, ataxia which had none of the other features of Machado-Joseph. One of the families came from the Bretanha region where there is a high concentration of the peripheral form of the disease.

We also recognized on São Miguel a large family with essential tremor, many members of which also had sufficient rigidity and slow resting tremor to be called Parkinson's disease. One branch of this family is closely allied to one of the Machado-Joseph kindred and the combination of symptoms may have been a source of confusion in previous observations.

Finally we also observed some cases of oculo-pharyngeal-muscular dystrophy presenting all the classical symptoms. It is thus important to beware of the trap of considering all historically reported incidences of "neurological disease" within a given kindred as examples of the disorder under study even in such closely-knit populations, particularly in view of the fairly high rate of consanguinous mariages in that population.

Discussion

The above cross-section study of 138 personally examined cases of Machado-Joseph disease has permitted a statistical and clinical analysis of this new disorder, with answers being provided for most of the previously grey areas of understanding. The protocole we have scrupulously followed in the investigation of each of the cases, whether examined at home or in special clinics, permits statistical and computer treatment of more than 48 items of the neurological examination and many other demographic data. This approach had previously been validated in the study of Friedreich's ataxia (Pourcher and Barbeau, 1980) and presents the advantage of being simple, reproducible and least subject to interobserver variability.

A. Definition of the Disease

From such analyses we are now able to state categorically that the entity under study is a single disease with a wide spectrum of clinical presentation forming a continuum. It is without any doubt an inherited malady, and all the kindreds studied indicate an autosomal dominant mode of transmission, demonstrated in some cases over more than eight known generations. There is no preponderance of cases for any given sex, nor is the sex of the affected parent a factor in either the mode of transmission or in the clinical expression.

In most cases the onset occurs between the ages of 20 and 40, with a certain proportion of patients at both extremities of the curve. The main clinical component of the disease is a progressive ataxia which is first manifested by stumbling and incoordination of gait and very slowly progresses to the other limbs and to dysarthria. Eye movement anomalies can be observed early and also progress with time, but for a long period, they are not of a severe nature. In a certain proportion of patients the external ophthalmoplegia is accompanied by a marked exophthalmia often as severe as that seen in hyperthyroidism.

The progressive ataxia, although eventually accompanied by a severe neuropathy, atrophy, fasciculations and muscle weakness,is not due to dorsal column and dorsal root ganglion damage, like that found early in Friedreich's disease. Even in

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the presence of a normal age of onset (20-40), the tendon reflexes are at first normo - or hyperreflexic and it is only after many years of progression that the tendon reflexes decrease or disappear and that vibratory sensation is appreciably impaired. In this respect patients with Machado-Joseph disease resemble what used to be called "Pierre Marie's spinocerebellar degeneration".

Variations in the age of onset, which appear to follow kindred homogeneity and may thus also be inherited (independently or not ?) will be the main determinants of the clinical expression of the secondary features of the disease. Whereas incoordination is present in almost all cases, even early, early onset of the disorder will be accompanied by evidence of hyperreflexia, pyramidal damage, increase in muscle tone even to the point of spasticity and clonus with a "Gegenhalten" phenomenon. It is of interest to note that this presentation pattern is also the rule, rather than the exception, in infantile and juvenile onset forms of lysosomal enzyme defects with storage disorders, while later onset is often accompanied in these diseases by cerebellar, extrapyramidal or amyotrophic signs. The later the onset in storage disorders, the more involvement of the spinal cord and peripheral nerves will be present. It is as if each age in life had its special area of vulnerability within the central and peripheral nervous systems, independent of the specific metabolic derangement to the homeostatism of the cell. If the patient escapes the early period during which spasticity develops, it almost never becomes a major feature in later years, even towards the end of life.

In Machado-Joseph disease both a late age of onset and many years of progression will instead favour severe involvement of the periphery in addition to severe incoordination. Muscle weakness, distal amyotrophy and, for a while, fasciculations become the rule, the latter disappearing when the muscle mass is markedly reduced. With age of onset after 50 it is possible to forego most of the marked progression in incoordination and to retain only the signs of motoneuron and peripheral nerve involvement. This explains why many patients were essentially unaware that they were victims, and why it is possible, when obtaining a retrospective family history, to have apparent skipping over of one or more generations.

In most patients the disease will progress to some degree of severe functional disability, but luckily it does not seem to involve superior cortical functions. In the typical pattern, death will occur after 10 to 15 years of steady progression, usually from intercurrent infections, but it is not unusual to observe survivals of 30 and 40 years.

From the above description we would like to propose criteria for the diagnosis of Machado-Joseph disease, slightly updated from those of Lima and Coutinho (1980). These are listed in Table 19.

Table 19: Machado-Joseph Disease Diagnostic Criteria*

1. Always an *autosomal dominant* mode of inheritance
2. *Major* neurologic picture characterized first by a *progressive ataxia* and secondarily by a progressive *amyotrophy* (Phenotype II — "typical")
3. Little progressive *pyramidal* signs can be associated in variable degree with a spastic-akinetic syndrome when the age of onset is low (Phenotype I), or with a peripheral amyotrophy and fasciculations in late onset cases (Phenotype III). [Clinical phenotypes form a continuum and are mainly determined by age of onset and by the place of origin of the kindred]
4. *Minor signs* (inconstant but specific when present) such as progressive external ophthalmoplegia (including gaze paresis and abnormal saccades), dystonic posturing, intention facial and lingual fasciculations or myokymia, vibratory sense loss, and bulging eyes

* Modified from Lima and Coutinho (1980) to take into account findings of present study

B. Nosological Classification

It is always difficult to classify inherited ataxias, particularly when there is heterogeneity of presentations. It used to be said that only a pathological classification would be valid (Greenfield, 1954), but even these criteria fail to withstand the test of time, cases from the same kinship often having a significantly different pathology.

We can recall that even in the present disorder the early studies favoured heterogeneity because pathologists could not agree on a common description of the anatomic lesions. There is now more agreement (Sachdev et al., 1982) on the neuropathology of Machado-Joseph disease: in contrast to OPCA, the cerebellar cortex and olivary nuclei are consistently spared. Neuronal loss is always and uniformly present in the dentate nucleus, in the substantia nigra, in the anterior horns and in Clarke column, with more variable involvement of pontine and cranial nerve nuclei. The initial denomination of striato-nigral degeneration proposed by Rosenberg (1977b) is now less probable.

Many clinical classifications have been proposed over the years, none totally satisfactory (this subject will be reviewed by us elsewhere). We have recently proposed a functional classification based on the criteria of progression, of age of onset and on certain elements of clinical descriptions (Barbeau, Sadibelouiz and Roy, 1984, this issue). As it concerns autosomal dominant hereditary ataxias, this classification is reproduced in Table 20. Greenfield (1954) had clearly defined the categories of pure cerebellar ataxias which include the so-called Holmes ataxia and late cortical cerebellar atrophy more popular in the Japanese literature. Pure spino-cerebellar ataxias of dominant inheritance are much less frequent. In 1969, Mars and collaborators had described a large family with ataxia in whom the affected subjects were found to have hypo-β-lipoproteinemia, thus resembling the recessive form of the disease (Bassen-Kornzweig disease). Some years ago, one of the present authors (Barbeau and Giroux, 1972; Giroux and Barbeau, 1972) had the occasion of describing a new entity characterized by neurocutaneous signs (erythrokeratodermia) and a late appearing spino-cerebellar ataxia. Most other cases of autosomal dominant hereditary ataxias are almost impossible to classify pathologically because they typically involve more than one system, often in a progressive way. Because of this, we propose to utilize the term Multi-System Degeneration for this "mixed-bag" of cases. Recently authors have started using the designation "Parkinsonian multisystem degenerations" for a multitude of entities involving the brain stem and encroaching upon the substantia nigra. In a similar vein we would like to propose the term "Ataxic multisystem degenerations" to designate hereditary entities involving the brain stem but encroaching upon the cerebellun and its afferent pathways. Most of the olivo-ponto-cerebellar atrophies

Table 20: Progressive Hereditary Ataxias of Autosomal Dominant Inheritance — A Functional classification

A — PURE CEREBELLAR ATAXIAS
- (1) HOLMES
- (2) LATE CORTICAL CEREBELLAR ATROPHY

B — PURE SPINOCEREBELLAR ATAXIAS
- (1) HYPO-ß-LIPOPROTEINEMIA (Mars)
- (2) ATAXIC ERYTHROKERATODERMIA (Barbeau and Giroux)

C — ATAXIC MULTI-SYSTEM DEGENERATIONS
- (1) OPCA
- (2) OPCA — TYPE WADIA-SWAMI (with slow saccades)
- (3) OPCA + RETINAL DEGENERATION
- (4) MACHADO-JOSEPH DISEASE
- (5) DENTATO-RUBRO-PALLIDO-LUYSIAN ATROPHY

(OPCA) as defined by Konigsmark and Weiner (1970), would fall within this category. As pointed out by Harding (1981) the OPCA's with retinal degeneration form a distinct hereditary group, so would the families from India described by Wadia and Swani (1971).

It is our proposition that Machado-Joseph disease belongs to this general category. It is not impossible that, when the genes for these disorders are finally identified and sequenced, it will be found that some are in fact allelic, within the broad classification of the "Ataxic multi-system degenerations".

Conclusion

The entity first described independently by Nakano et al. (1972), Woods and Schaumburg (1972) and Rosenberg et al. (1976), is in fact a single disease. For historical reasons it should be called "Machado-Joseph Disease". It is an inherited disease with an autosomal dominant pattern. We would like to propose that it is an inherited "ataxic multi-system degeneration", presenting as a progressive ataxia with external ophthalmoplegia. When the age of onset is earlier than the usual range of 20 to 40 years, the disease present with marked spasticity of a non progressive nature, but often so severe that it can be accompanied by Gegenhalten countermovements, akinesia and dystonic postures, but no frank dystonia or rigidity. When the disease starts after the age of 50, the clinical picture is mostly that of an amyotrophic polyneuropathy with fasciculations. For all the other cases the clinical picture is a continuum between these two extremes, the main determinant of the clinical phenotype being the age of onset. The ataxic and amyotrophic components are clearly progressive with time. Although the majority of cases are of Portuguese origin, this is not obligatory and it is likely that other similar kindreds will be identified in other ethnic groups.

Now that the unity of the disease is established without any doubt, partly through the data accumulated in the course of the present study, it will be important to use the new methodologies of molecular biology to find the "M-J" gene and sequence it. This should be the main research effort of the next few years, particularly since the availability of clinical material from the same source is not a major problem, and now that heterogeneity of the "Machado" and "Joseph" forms is excluded.

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Appendix

Comments about some of our conclusions have been made by a few collaborators and deserve to be aired for further discussion and investigation:

(1) The picture of the disease as seen in a given locale by a given observer is highly subject to observer bias. This may explain the historical initial divergences in description.

(2) In the U.S.A. clinics, both on the East and West Coasts, no effort was made to accomplish complete ascertainment of the cases. Only the patients who can travel, and primarily the patients who are interested in the disease, will show up at clinics of that type. Other patients, perhaps with other clinical forms, may exist and would be missed.

(3) Some observers disagree with us on the low prevalence of extrapyramidal signs. We accept this possibility, but must restate that none of the 138 patients the two senior authors examined could so be classified. The perplexing finding of moderate to severe substantia nigra damage in most cases reviewed is still not well explained.

(4) Some collaborators feel that the neuropathologic variability may be as significant as the clinical variations (see Coutinho et al., 1982; Sachder et al., 1982). We agree, and further stress that the initial apparent confusion was again a manifestation of the phenomenon of observer bias.

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