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Caring for Machado-Joseph Disease: current understanding and how to help patients

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Abstract

Machado-Joseph disease or spinocerebellar ataxia 3 (MJD/SCA3) is a clinically heterogeneous, neurodegenerative disorder characterized by varying degrees of ataxia, ophthalmoplegia, peripheral neuropathy, pyramidal dysfunction and movement disorder. MJD/SCA3 is caused by a CAG repeat expansion mutation in the protein coding region of the *ATXN3* gene located at chromosome 14q32.1. Current hypotheses regarding pathogenesis favor the view that mutated ataxin-3, with its polyglutamine expansion, is prone to adopt an abnormal conformation, engage in altered protein-protein interactions and aggregate. Expanded CAG repeat length correlates with the range and severity of the clinical manifestations and inversely correlates with age of disease onset. Though MJD/SCA3 is classically described as affecting the cerebellum, brain stem and basal ganglia, recent neuropathology and neuroimaging series demonstrate involvement of other areas such as the thalamus and cerebral cortex. Clinically, much emphasis has been placed in the description and recognition of the non-motor symptoms observed in these patients, such as pain, cramps, fatigue and depression. Currently, no disease modifying treatment exists for MJD/SCA3. Standard of care includes genetic counseling, exercise/physical therapy programs, and speech and swallow evaluation. Symptomatic treatment for clinical findings such as depression, sleep disorders, parkinsonism, dystonia, cramps, and pain is important to improve the quality of life for those with MJD/SCA3.

Keywords

Spinocerebellar ataxia type 3; SCA3; Machado-Joseph disease; CAG

Introduction

The first description of Machado-Joseph disease or spinocerebellar ataxia type 3 (MJD/SCA3) occurred in 1972 in a family of Portuguese immigrants in Massachussets, who presented a hereditary ataxia characterized by subacute onset of ataxia after age 40 associated with end-gaze nystagmus, mild dysarthria, hyporeflexia and distal muscle atrophy [1]. Though not clear at the time, the authors believed the disease to follow an autosomal dominant inheritance

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pattern. Two other families were later described under a different clinical syndrome and name [2,3]. In 1977, Romanul described a fourth family of Azorean descent with a progressive neurodegenerative disorder and suggested that the previously described families represented clinical spectra of the same disease [4]. In the following years, the disease was described in different countries and populations without Azorean ancestry [5]. The history of the description of the disease highlights the two fundamental points of the disease: autosomal dominant inheritance and marked clinical heterogeneity.

Although MJD/SCA3 is a relatively rare disease, it is the most frequent spinocerebellar ataxia with a worldwide distribution [5]. Its prevalence, however, varies according to the population studied. In this review, we aim to address classical aspects of MJD/SCA3 pathophysiology and clinical manifestations, placing a special emphasis on recent developments in the understanding of the disease..

Genetics of Machado-Joseph: an overview

The locus responsible for MJD/SCA3 was mapped to chromosome 14q32.1 in 1993, and the causative gene, now termed *ATXN3*, cloned in the following year [6]. In all patients with MJD/SCA3 reported so far, the mutation found is a trinucleotide repeat expansion (CAG) located in the 10^{th} exon [6], which leads to an abnormally long polyglutamine (polyQ) tract in the encoded protein, ataxin-3. Thus, the molecular genetic basis of MJD/SCA3 is similar to that in SCAs1, 2, 6, 7, 17, Huntington disease and spinobulbar muscular atrophy, which are collectively referred to as polyQ disorders.

In polyQ disorders, disease develops when the (CAG) repeat size exceeds a threshold length. This threshold varies among polyQ disorders; in MJD/SCA3, pathogenic alleles have larger than approximately 51 repeats at *MJD1* [6]. In MJD/SCA3, the normal alleles range between 12 and 47 repeats. In rare instances, (CAG) repeat count falls into the 47 and 51 interval (intermediate alleles). These alleles are probably associated with an increased risk of developing clinical disease, but penetrance is incomplete (in contrast to the typical alleles with >51 repeats). Homozygosity for (CAG) repeat expansions at *MJD1* is another rare situation, but the few reported cases do seem to present much more severe phenotypes than what is observed in heterozygous individuals [7]. Thus, a dosage effect may be present in MJD/SCA3.

Mutations responsible for polyQ disorders are unstable: the repeat length of an expanded allele frequently changes during parental transmission. The trend is toward increased repeat length in successive generations, which clinically translates in the clinical phenomenon of anticipation; i.e., the tendency for earlier disease onset and more severe phenotype in successive generations [8].

In some polyQ disorders, disease-causing expansions can arise de novo from intermediate alleles resulting in "sporadic" cases of disease (i.e., without family history). This has not formally been demonstrated in MJD/SCA3, and most patients do in fact describe a positive family history.

Gene structure and protein function

Ataxin-3 is a 42 kDa, widely expressed protein that resides both in the nucleus and cytoplasm of cells. It has been implicated in many aspects of intracellular protein quality control pathways that rely on the small modifer protein, ubiquitin. Ataxin-3 is a deubiquitinating enzyme (DUB) that cleaves ubiquitin from ubiquitinated substrates or poly-ubiquitin chains [9]. The details of ataxin-3's action as a DUB are still uncertain, but it may prefer to cleave "nonstandard" ubiquitin linkages and assist ubiquitin ligases in generating specific types of ubiquitin chains

on substrates [10]. Another proposed role for ataxin-3 is in transcriptional regulation [11] though how this relates to its enzymatic action as a DUB is unknown.

Despite recent progress in the functional characterization of ataxin-3, there is not yet a perfect model explaining molecular pathogenesis of MJD/SCA3. One current hypothesis posits that polyglutamine expansion interferes with ataxin-3 DUB function in some manner that compromises one or more biochemical pathways dependent on ubiquitin, including the ubiquitin-proteasome protein degradation system. A consequence would be misfolding and aggregation of proteins in vulnerable neurons. MJD-intranuclear inclusions, present in select brain regions in the human disease, are a neuropathological expression of these phenomena. Although recent evidence suggests that ataxin-3 inclusions are not toxic *per se*, the accumulation of misfolded and aberrant, nonfunctional proteins above a threshold level is likely a key component to neuronal toxicity [12]. In this setting, nuclear inclusions may actually have a protective role related to the sequestration of the abnormal proteins [13].

Genotype-phenotype correlation

Several aspects in the phenotype of MJD/SCA3 correlate to the length of the expanded (CAG), with most reports describing a strong inverse relationship between CAG repeat length and age at onset [8,14](see figure 1). The length of repeat expansion accounts for 50–60% of the variability in age of disease onset. Furthermore, the larger the expansion the greater its influence on age at onset. Other factors certainly contribute to variability in the age at onset in MJD/SCA3. A previous study showed that a familial factor independent of the mutation itself influenced the age at onset [15]. Longer expanded (CAG) repeats are also associated with a higher frequency of pyramidal and dystonic manifestations in MJD/SCA3 [14]. In a large study of SCAs, MJD/SCA3 patients with larger repeats and earlier age at onset presented more spasticity and hyperreflexia. In contrast, peripheral neuropathy is mostly related to higher age and disease duration. SARA scores were mostly determined by disease duration, age at onset and CAG length of the expanded allele. Higher scores also increased the risk of non-ataxia symptoms [16].

Neuropathology

A recent published paper systematically evaluated terminal MJD/SCA3 patients with unconventional thick serial tissue sections in addition to conventional neuropathological studies [17]. Their findings demonstrated gray matter degeneration in multiple areas involved in the cerebellothalamocortical motor loop; the basal ganglia-thalamocortical motor loop; the visual, auditory, somatosensory, oculomotor and vestibular system; the ingestion-related and precerebellar brainstem system; the pontine noradrenergic system and the dopaminergic and cholinergic midbrain system. White matter degeneration was restricted to the cerebellum, spinal cord and brainstem. This more comprehensive understanding of MJD/SCA3 neuropathology better explains a variety of its symptoms, especially the non-motor ones.

Neuroimaging studies

Figure 2 demonstrates typical imaging findings in patients with MJD, though minimally symptomatic patients or patients with new-onset symptoms may present with normal MRIs. The first large series of molecularly confirmed MJD/SCA3 patients studied by magnetic resonance imaging (MRI) included 31 MJD/SCA3 patients, 20 patients with sporadic olivopontocerebellar atrophy, and 26 control subjects [18]. The authors measured the anteroposterior and transverse diameter of different structures of the brainstem, cerebellum and globus pallidum, and graded semi-quantitatively the atrophy in the cerebral hemispheres with a scale from 0–3 (none-severe). The main findings were severe atrophy of the pons, middle and superior cerebellar peduncles, frontal and temporal lobes, and the globus pallidus, as well

as decreased anteroposterior and transverse diameters of the midbrain and decrease anteroposterior diameter of the medulla oblongata. The atrophy of the pons or midbrain was age-dependent while duration of illness correlated with the decrease in the anteroposterior and transverse diameters of the globus pallidus and with the degree of temporal or occipital lobe atrophy. A high signal intensity in the transverse pontine fibers was observed in 14 (45.2%) of 31 patients with MJD/SCA3.

The rate of atrophy progression in the cerebellum and brainstem is probably dependent both on the length of expanded (CAG) repeat and the patient's age [19,20]. The progression of atrophy, however, does not seem to be the same for different brain regions In a longitudinal study of 7 patients, while the atrophy of the pontine base and cerebellum significantly correlated with age, the atrophy in the midbrain and pontine tegmentum showed no progression [21].

Recent studies demonstrated that areas other than the cerebellum, brainstem, spinal cord and basal ganglia are also involved. Brain SPECT demonstrated perfusion abnormalities in the parietal lobes, inferior portion of the frontal lobes, mesial and lateral portions of the temporal lobes, basal ganglia, and cerebellar hemispheres and vermis [22]. The 18F-Dopa uptake in MJD/SCA3 was found to be significantly decreased not only in the regions with apparent pathological involvement such as cerebellum, brainstem and nigro-striatal dopaminergic system, but also in the cerebral cortex and the striatum where no pathology could be observed using conventional morphological techniques [23]. Magnetic resonance spectroscopy (MRS) of the deep white matter demonstrated changes suggestive of axonal dysfunction, even though there was no obvious anatomical alteration by visual MRI analysis [24]. A PET with fluorine-18-fluorodeoxyglucose (FDG) study in seven asymptomatic MJD/SCA3 patients showed subclinical changes of FDG consumption decreased in the cerebellar hemispheres, brainstem, and occipital, parietal and temporal cortices of asymptomatic MJD/SCA3 gene carriers, suggesting preclinical disease activity [25].

Clinical Manifestations

Clinical subtypes

As described previously, MJD/SCA3 is characterized by remarkable phenotypic heterogeneity. However, specific clinical features are often clustered in the same patient. Classically, patients with MJD/SCA3 may be grouped into five clinically defined subtypes (see Table 1) [5,26]. This clinical classification is not strictly demarcated and some patients do not perfectly fit into one of these subtypes, thus rendering this subdivision not particularly useful.

Motor manifestations

Most patients first notice disability in the 3rd or 4th decades due to cerebellar ataxia, which follows a relentlessly progressive course. Gait instability generally dominates the clinical picture, but signs of limb incoordination are also common [27]. Intentional tremor may be prominent in some individuals. Scanning speech, dysphagia and truncal ataxia are also typical of MJD/SCA3, but tend to develop later.

Oculomotor abnormalities collectively represent important and frequent findings. In MJD/SCA3, the most common visual or ocular complaints is diplopia [27], which is usually first noticed when patients read. On examination, one can see gaze-evoked nystagmus, abnormal saccades, decrease smooth pursuit gain, impaired vestibulo-ocular reflex and supranuclear vertical gaze palsy [28]. Another sign, more common in MJD/SCA3 patients than in any other SCA, is the "bulging eyes appearance" due to the combination of lid retraction and poor blinking [27].

Pyramidal dysfunction is common in MJD/SCA3, especially in individuals with early onset and large (CAG) repeat expansions [14]. Legs are more affected than arms, and spasticity rather than true weakness tends to predominate [27]. There are occasional reports of spastic paraplegia as the first or only manifestation of MJD/SCA3 [26]. Features of pseudobulbar syndrome are found in around 15% of patients [27].

Two distinctive movement disorders are frequent of MJD/SCA3: dystonia and parkinsonism [5,14]. Dystonia is mostly found in early onset patients, and is sometimes task-specific. It can be focal, segmental, or generalized (resembling idiopathic torsion dystonia) [29]. DOPA-responsive forms [30] have been described as well, thus any person with MJD/SCA3 and dystonia deserves a trial of a dopaminergic agent. Parkinsonism, expressed by bradykinesia and rigidity, is much less frequent than dystonia, but may respond dramatically to L-DOPA [31]. Patients with parkinsonian-phenotype often have symmetric manifestations; resting tremor is not a universal feature but can be seen. In persons with strong family history of parkinsonism and gait imbalance, MJD/SCA3 must be considered in the differential diagnosis Peripheral nerves are involved in approximately 60% of patients with MJD/SCA3 [32].

In contrast to dystonia and spasticity, peripheral neuropathy is mostly determined by duration of disease and thus is found in older individuals [16]. Sensory fibers are most frequently affected. In most cases, there are widespread areas of tactile and proprioceptive hypoesthesia rather than the usual stocking-and-glove pattern of dying back neuropathies. Neuropathic pain occurs occasionally. Damage to motor fibers may cause muscle atrophy, distal weakness with foot drop and fasciculations, which may further aggravate motor handicap. Autonomic manifestations are also common, especially those related to the genitourinary (nocturia, urinary incontinence) and sudomotor (cold intolerance, hypohidrosis) systems [33]. Although orthostatic hypotension has been reported, it is not often a major complaint.

Non-motor manifestations of MJD/SCA3

Previous paragraphs addressed motor aspects of MJD/SCA3. However, late reports point to important non-motor symptoms and possibly under-recognized manifestations of the disease [34,35,36,37,[38],39,40,41,42] Sixty percent of patients with MJD/SCA3 have excessive daytime sleepiness, due in most cases to impaired nocturnal sleeping [34]. Older age and long disease duration are associated with sleep complaints. In addition, two specific, sleep related disorders are often found in MJD/SCA3: restless legs syndrome and REM sleep behavior disorder. Restless legs syndrome is frequent in MJD/SCA3 (50% of patients), but not in other SCAs [35]. REM sleep behavior disorder, in which dreaming is not accompanied by muscle atonia during REM sleep, leads to disturbed night sleep and, on occasion, harm to the patient. Increasingly recognized in MJD/SCA3, REM sleep behavior disorder can be a treatable cause of disordered sleep. Patients also often complain of insomnia [36].

Although frank dementia is not a common feature of MJD/SCA3, minor cognitive and behavioral abnormalities do occur. Formal neuropsychological studies are few, and results must be cautiously interpreted since patients have severe motor disability. Verbal and visual memory deficits, visuospatial dysfunction and executive dysfuction have all been reported in MJD/SCA3 [37,38]. Depressive symptoms are also common [39]. Psychotic symptoms are not frequent, but several of us (AD, MCFJr, ILC) recently saw two patients with delusional thinking and disinhibited behavior, characteristic of frontal lobe dysfunction.

Chronic pain was found in roughly 50% of patients with MJD/SCA3, and lumbar region was the major involved site [40]. Pain is probably multifactorial and classified as musculo-skeletal in most patients. Cramps are a frequent and disabling symptom in patients with MJD/SCA3 [41]. In a sample of 50 patients, 15 (30%) considered disabling cramps their chief complaint

[41]. A recent report demonstrated a high prevalence of fatigue in MJD/SCA3, around 60%, which was more severe in patients with longer disease duration [42].

Clinical course

Although clinical features of MJD/SCA3 have been extensively reviewed, there are few data on the natural history of MJD/SCA3. Ataxia is the usual first symptom, beginning in the 3rd or 4th decade, and progresses slowly thereafter. In a cross-sectional study from Brazil, authors estimated mean survival time of 21 years after disease onset [43]. They also found that earlier age at onset and larger (CAG) repeat expansion were predictive of shorter survival.

Diagnosis

Diagnosis is made based on clinical features, family history and genetic testing. In anyone with a neurodegenerative syndrome, a thorough review of family history is extremely helpful and mandatory. Although some clinical findings may strongly suggest the diagnosis of MJD/SCA3, there are no pathognomonic clinical or neuroimaging findings. In individuals with a neurodegenerative ataxic syndrome and molecularly confirmed MJD/SCA3 in the family, selective genetic testing for the MJD/SCA3 mutation is appropriate and should clinch the diagnosis. Molecular genetic testing is widely available and is highly sensitive and specific. In contrast, for individuals with a family history of similar disease but no prior genetic testing, more broad-based genetic testing that screens a panel of SCAs should be considered. In persons without a clearcut family history, further ancillary testing should be considered on an individual basis to rule out other treatable systemic and neurologic disorders. Presymptomatic predictive genetic testing programs following published international guidelines, are available worldwide [44]. Studies demonstrated that adverse events do not occur in predictive testing of at-risk persons when guidelines are followed.

Treatment

MJD/SCA3 is a steadily progressive neurodegenerative disease with no specific treatment. The following recommendations are mostly derived from other neurodegenerative diseases a nd our personal experience in caring for a large number of patients with MJD/SCA3.

Initially, it is imperative to provide adequate genetic counseling to patients and immediate family members. Patients should be informed of the nature of the disease, the risk to other family members, and the current lack of disease modifying therapies. At risk family members should be aware of the availability of predictive testing for those interested. Prenatal diagnosis is also available in some countries.

We believe every patient should be enrolled in an exercise program after physical therapy evaluation. In Parkinson disease (PD) exercising is beneficial to physical functioning, health related quality of life, strength, balance and gait. Even though we cannot affirm that exercise slows disease progression, we believe it helps patients better cope with their disabilities [45]. In our experience, exercise also seems to increase self-esteem and boost patients' mood and sense of control over their disease. They should also undergo regular speech therapy evaluation for dysarthria and dysphagia. Some also benefit from occupational therapy.

Symptomatic treatment is available for a wide range of symptoms, even though most symptomatic medications have not been studied in this specific population. Depression should be treated with antidepressants and/or therapy and possibly a referral to a psychiatrist. Sleep related symptoms warrant polysomnographic studies if available and treatment accordingly. A recent published diagnostic criteria for RLS may be useful in situations where polysomnography is not available [46], especially if associated with careful exclusion of confounding factors including prevalent symptoms in MJD such as cramps, peripheral

neuropathy and pain [47]. We also advise proper work up of patients with RLS, even though they are most likely primary in nature. Primary RLS are usually managed with dopamine agonists and levodopa [48]. Pain is often multifactorial and attempts should be made to better identify if it is musculoskeletal, neuropathic, secondary to dystonia or mixed. This will better guide medication selection and hopefully provide a more satisfactory clinical response. Cramps may be treated with mexiletine or carbamazepine [40,41] We also follow the general recommendations for the treatment of fatigue in neurological diseases, mostly the PD literature. Treatment is divided into pharmachological (methylphenidate, modafinil and amantadine) and non-pharmacological interventions (patient and caregiver education, behavioral modification, physical actitivity) [49].

Parkinsonism, dystonia and spasticity are managed as in other neurologic disorders. As mentioned earlier, some patients with MJD have levodopa-responsive dystonia, hence all patients with dystonia should undergo a trial of the medication. Other options include anticholinergics, benzodiazepines, baclofen and carbamazepine [50]. Botulinum toxin (BonT) injections might be helpful in focal or segmental cases. There are no reports in the systematic evaluation of the clinical use of BonT injections in patients with MJD and we do not have large experience with BonT in these patients. Ophthalmologic consultation for prisms may help with diplopia.

As the disease progresses, safety measures to avoid falls should be implemented at home. Patients experiencing falls should be evaluated for the appropriate assistive devices. A not uncommon issue in our outpatient clinic is resistance to the use of assistive devices. Patients should understand that the use of walkers and wheelchairs do not mean they are "giving up", but rather, adjusting to disease progression, maintaining their safety, avoiding fractures and mostly for some, keeping their independence.

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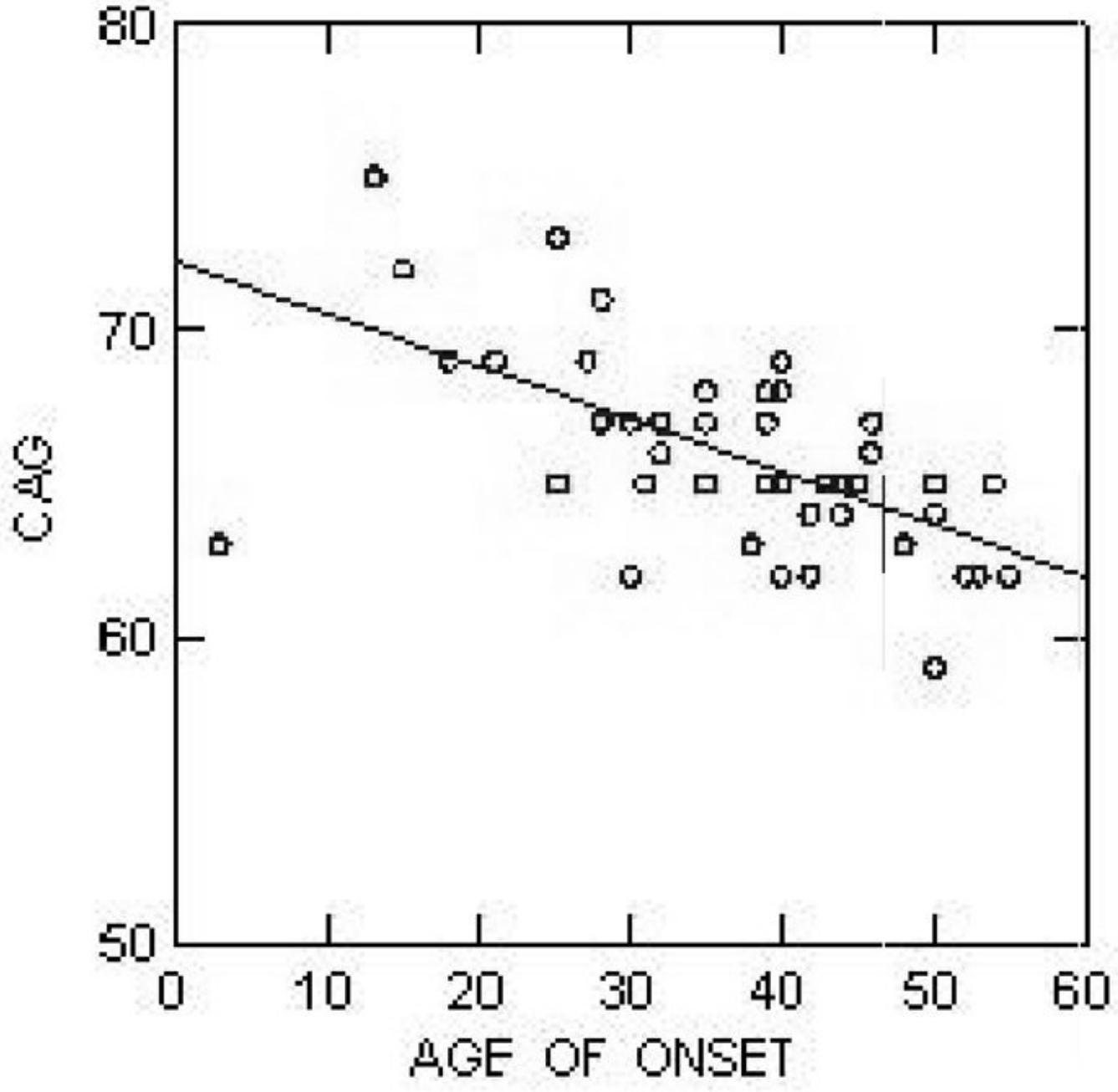

Figure 1.
Negative inverse correlation between CAG repeat length and age of onset. In this specific sample r= −0.6; p<0.001.
Inverse correlation between age of onset and CAG repeat lenght.

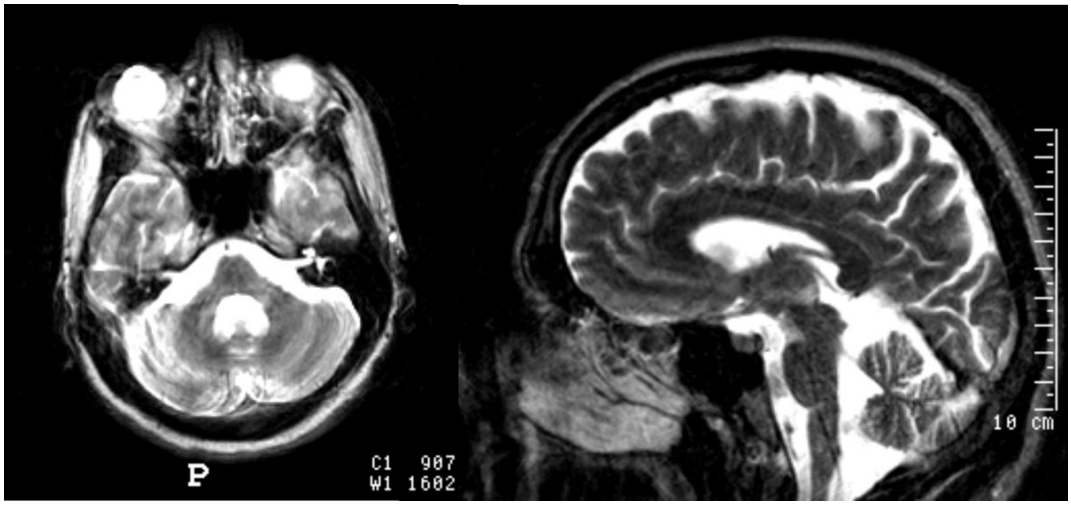

Figure 2.
MJD patient (age: 54 years; disease duration: 29 years) demonstrates cerebellar and brainstem atrophy.
Left: Axial view: atrophy of the cerebellum and cerebellar peduncles. Right: Sagital view: Marked atrophy of the brain stem and cerebellum.

Tabela 1

Classical Clinical Subtypes in MJD/SCA3

Clinical Subtype	Clinical Characteristics
I	Earlier onset, axial ataxia associated with prominent dystonia and spasticity.
II	Prominent axial ataxia and occasional leg spasticity. This is the most frequent phenotype in the disease, manifesting typically in mid adult years.
III	Later onset, ataxia and peripheral neuropathy, expressed by distal muscle atrophy and areflexia.
IV	Parkinsonian phenotype; does not map to any particular repeat length or age of onset.
V	"Pure" progressive spastic paraplegia. Such cases are very rare and share many features with those in subtype.