A rare type 4 phenotype of Machado–Joseph disease with Parkinsonism

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ABSTRACT

Background: Machado–Joseph Disease (MJD) also known as Spinocerebellar Ataxia3 or Azorean ataxia is a progressive autosomal dominant neurological disorder which affects cerebellum and its function that leads to ataxia and incoordination of gait.

Case Presentation: A 20-year old male presented with chief complaints of abnormal posturing of both lower and upper limbs, slurred speech, and a nasal regurgitation. Neurological examination revealed gaze evoked nystagmus, spasticity in both lower limbs which are indicative signs of cerebellar dysfunction. Genomic DNA analysis was performed, and patient condition was diagnosed as MJD with Parkinsonism.

Conclusion: Patient was treated symptomatically with medications and physiotherapy to relive symptoms of Parkinsonism. After a week of follow-up, his symptoms were subsided and got discharged.

Keywords: MJD, autosomal dominant, Ataxia, Parkinsonism, cerebellar dysfunction.

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Background

Machado–Joseph Disease (MJD) otherwise known as Spinocerebellar Ataxia3 (SCA3) is an autosomal dominant neurological disorder characterized by Progressive cerebellar ataxia and incoordination of gait. Sometimes it appears as a dystonic-rigid syndrome associated with Parkinsonism features. This condition was mainly due to the abnormal Cytosine, adenine, guanine (CAG) trinucleotide repeat expansion in a Ataxin-3 gene (ATXN3) [1]. There exist usually three phenotypes of MJD as type 1 with pyramidal and extra-pyramidal signs, type 2 characterized by cerebellar and Pyramidal signs, type 3 associated with cerebellar signs and anterior horn cell degenerative symptoms, and finally fourth variant as Parkinsonism with cerebellar dysfunction [2]. Hereby we report a case of rare type 4 phenotype of patient with MJD associated Parkinsonism.

Case Presentation

A 20-year-old male patient was presented to Government General Hospital, Kadapa with the chief complaints of abnormal posturing of toes of both lower limbs, choreiform movement of both lower limbs, tightness of upper limbs and lower limbs, and tremulousness of right hand. He remains asymptomatic till 3 years back and symptoms started from past 1 year. Later on admission, he developed nystagmus, incoordination of gait, and nasal regurgitation of foods. His past medical history reveals no other health related illness. As his symptoms were getting worse, his blood sample was collected and sent for Genomic DNA analysis which revealed MJD with Parkinsonism. Magnetic resonance imaging (MRI) brain with screening of spine revealed cerebral atrophy (Figure 1).

On general examination, the patient was conscious and oriented, **PR—70/mt,** blood pressure —120/80 mm of Hg, respiratory rate —20/mt, Planta—Right and Left withdrawal sensory, cardiovascular system —S1S2 normal, and Lungs—Clear.

His laboratory investigations were normal except for **RBC—2.8 millions/Cu mm,** packed cell volume **(PCV)—33%**, others includes Sr. Creatinine—0.99 mg/dl, Sr. Sodium—139 mmol/l, Sr. Urea—20 mg/dl, serum glutamic oxaloacetic transaminase —24 IU/l, serum glutamate-pyruvate transaminase —17 IU/l, Sr. Alkaline phosphatase—69 IU/l, Albumin—4.3 gm/dl, Total protein—7.1 g/dl, total bilirubin—0.8 mg/dl, Conjugated bilirubin—0.1 mg/dl, Sr. creatinine kinase —80 IU/l, hemoglobin —15 gm%, Total count—8,400 cells/cu mm, erythrocyte sedimentation rate —8 mm/hours, Platelets count—2.70 lakhs/Cu mm, RBC—2.8 millions/Cu mm, PCV—33%, mean corpuscular hemoglobin—33 pg, random blood sugar —80 mg/dl, triiodothyronine —136.50 ng/dl, thyroxine —8.45 ng/dl, thyroid stimulating hormone —1.80 µIU/ml, human immune deficiency virus —Negative, hepatitis C virus —Negative, hepatitis B virus surface antigen —Negative, antistreptolysin O —195.57 IU/ml.

Following drug chart was used to treat the condition.

Table 1. Drug Regimen.

DRUG	DOSE	ROUTE OF ADMINISTRATION	FREQUENCY	NO OF DAYS USED
Tetrabenazines	25 mg	Oral	Once in day (OD)	Seven
Clonazepam	0.25 mg	Oral	OD	Seven
Trihexyphenidyl Hydrochloride	2 mg	Oral	OD	Seven
Levodopa and Carbidopa	100 mg	Oral	OD	Seven
Sodium valproate	500 mg	Oral	OD	Seven
Amantadine Hydrochloride	100 mg	Oral	OD	Seven

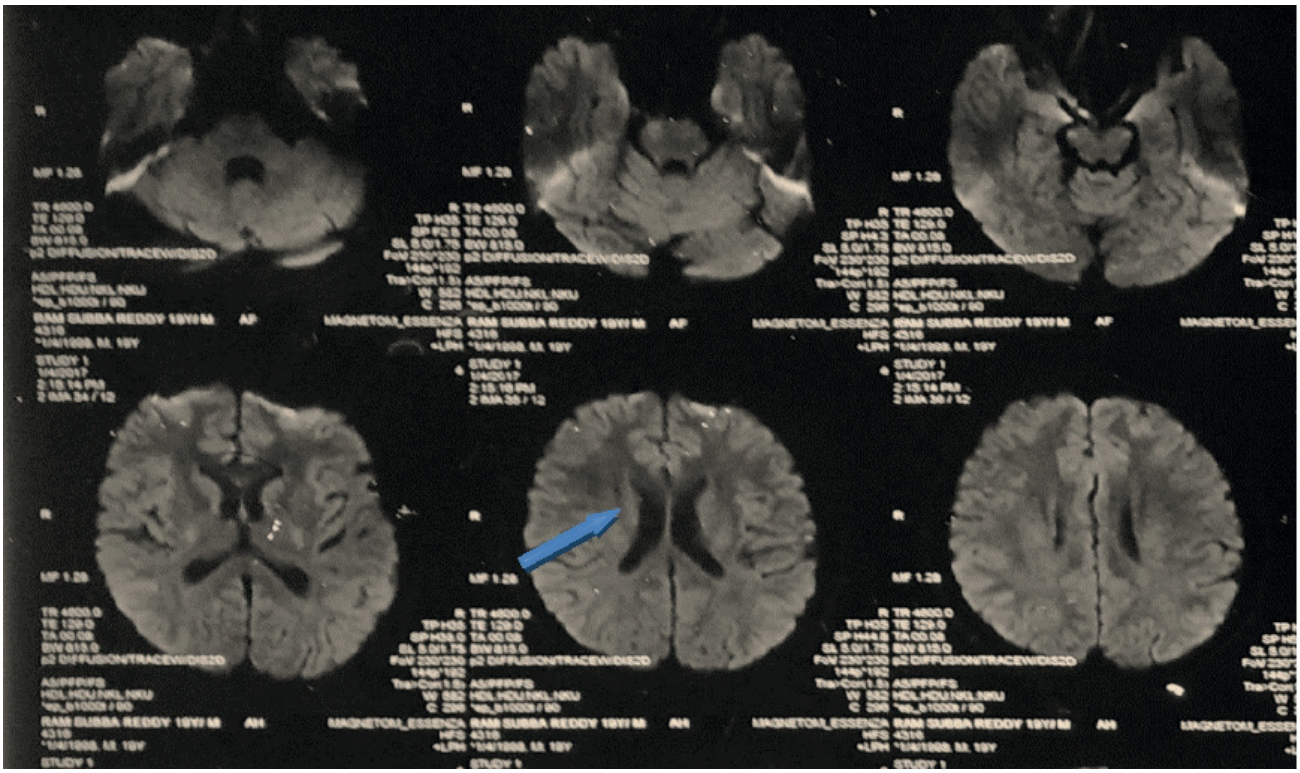

Figure 1. *Region of brain revealing cerebral atrophy.*

Table 2. Genomic DNA Analysis of patient showing CAG repeats.

LOCUS	ALLELE SIZE [bp]		NUMBER OF REPEATS	
	UPPER	LOWER	UPPER	LOWER
SCA1	208	204	28	27
SCA2	120	120	19	19
SCA3	397	256	79	32

SCA1 - Spinocerebellar Ataxia type 1
SCA2 - Spinocerebellar Ataxia type 2
SCA3 - Spinocerebellar Ataxia type 3
bp - base pair

Discussion

Parkinsonism with cerebellar dysfunction is a rare type 4 phenotype of MJD. It was first genetically confirmed SCA subtype in a patient with the levodopa-responsive Parkinson disease [3]. This condition was often caused by repeated expansions of CAG encoding the polyglutamine (poly Q) and had the pathological evidence of involvement of both basal ganglia and the substantia nigra with dopamine depletion associated with marked cell loss and gliosis in SCA2 and SCA3 [4]. In MJD genes that are affected were present on the chromosome no 14 with normal repeat size of about 12–40 but in this condition, there was expansion size of about 55–86 [5]. In our case the upper repeat size of CAG is 79 which is abnormal, heterozygous status for SCA1 and homozygous status for SCA2 (Table 2). Also, patient had a tremor which becomes slow as get progress and was observed in the distal and proximal regions hence termed as Orthostatic as described in the literature [6]. The condition was onset for the patient at an age of 20 years which was early, and his parents were acting as asymptomatic carriers in this case with autosomal recessive genes. The pathogenesis of Parkinsonism in MJD is mainly associated with the gene called Beta-glucocerebrosidase (GBA). Other protein that is related to ataxin-3 in the pathogenesis

of Parkinsonism is Parkin. Additive effect or mutations of both the genes ataxin-3 and GBA were independently associated with the manifestations of Parkinsonism in this patient as evident from the literature [7]. Finally, in all neurodegenerative disease's protein aggregation with expanded glutamine domain was the basis of disease. However, all the neurodegenerative diseases should not be misdiagnosed because protein aggregation was the basis but the repeated expansions of CAG or polyglutamine tract was observed only in the selective diseases like MJD [8].

Conclusion

It is very important to manage this condition with symptomatic therapy because there were more chances of death to patient due to further complications, such as aspirational pneumonia with dysphagia (Respiratory diseases), Ataxia, and Infectious diseases, like sepsis.

Hence, the patient was provided with the symptomatic relief and physiotherapy options to relieve the Parkinsonism features to prevent the further worsening of the condition. After the follow-up for a period of 1 week, he was found to be stable as Parkinsonism features were resolved and got discharged.

What is new?

Literature says that Machado Joseph disease with Parkinsonism is a rare type. In this manuscript the patient parents do not have any neurological disorders so it's something new that how the defective genes are carried to this patient.

List of Abbreviations

PCV Packed Cell Volume
RBC Red Blood Cells

Consent for publication

Written informed consent was taken from the patient.

Ethical approval

Ethical approval is not required at our institution for publishing an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	Male, 20-Year-old.
2	**Final diagnosis**	Machado-Joseph Disease with Parkinsonism.
3	**Symptoms**	Abnormal posture of both lower limbs, nystagmus, in coordination of gait and nasal regurgitation.
4	**Medications**	Oral symptomatic medications were prescribed.
5	**Clinical procedure**	Genomic DNA analysis and Magnetic Resonance Imaging was performed.
6	**Specialty**	Neurology.