Clinical Reasoning: A 60-Year-Old Man With Ataxia, Chorea, and Mild Cognitive Impairment

Atsuhiko Sugiyama, MD, PhD, Chikako Nishigori, MD, PhD, Mariko Tsujimoto, MD, PhD, Yaei Togawa, MD, PhD, and Satoshi Kuwabara, MD, PhD

Neurology® 2022;99:618-624. doi:10.1212/WNL.0000000000201065

Correspondence
Dr. Sugiyama
asugiyama@chiba-u.jp

Abstract

We describe the case of a 60-year-old man with a 16-year history of gait imbalance and a 15-year history of forgetfulness. The insidious onset and slow progression suggested that the disease was degenerative. Neurologic examination revealed cerebellar ataxia, chorea, and mild cognitive impairment. Brain MRI revealed prominent cerebellum atrophy and diffuse atrophy in the brainstem and cerebrum. Based on neurologic manifestations, an additional patient interview and skin examination were conducted. Photosensitivity and freckling in exposed areas, which the patient did not recognize as disease symptoms, were observed. Based on acute and chronic photosensitivity and DNA repair test results, a final diagnosis was made. In patients with cerebellar ataxia, chorea, and cognitive dysfunction of unknown etiology, clinicians should explore patients' history of photosensitivity and carefully examine the skin.

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From the Department of Neurology (A.S., S.K.), Graduate School of Medicine, Chiba University; Division of Dermatology (C.N., M.T.), Department of Internal Related, Kobe University, Graduate School of Medicine; and Department of Dermatology (Y.T.), Graduate School of Medicine, Chiba University, Japan.

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Section 1

A 60-year-old Japanese man with a medical history of diabetes presented with gradually progressive gait imbalance that began at 44 years of age and development of forgetfulness beginning at the age of 45 years. The patient did not drink alcohol in excess and reported no family history of similar symptoms or neurodegenerative disorders, and his parents were not consanguineous. There were no complaints of hearing loss or eye symptoms. His weight was 49 kg and height was 156 cm. He did not have microcephaly. The patient received a score of 28 of 30 on the Mini-Mental State Examination. He scored 86 of 100 on Addenbrooke's Cognitive Examination III (in Japanese,[1] ≤88 reflects mild cognitive impairment), with the following subscores: attention and orientation, 18/18; memory, 23/26; fluency, 7/14; language, 24/26; and visuospatial skills, 14/16. Cranial nerve examination was significant for the breakdown of smooth pursuits without nystagmus and mild cerebellar dysarthria. Involuntary choreiform movements of the tongue and upper and lower extremities were noted (Video 1). He had normal strength in both arms and legs. Deep reflexes in the lower limbs were absent. He had bilateral mild dysmetria and dysdiadochokinesia. His gait was normal, but tandem walking was impaired. Sensory examinations were normal. There was no Romberg sign. The Assessment and Rating of Ataxia Scale was used and indicated a score of 8.5.

Questions for Consideration:

1. What is the differential diagnosis for the patient's presentation?
2. What is your initial approach to investigations?

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Section 2

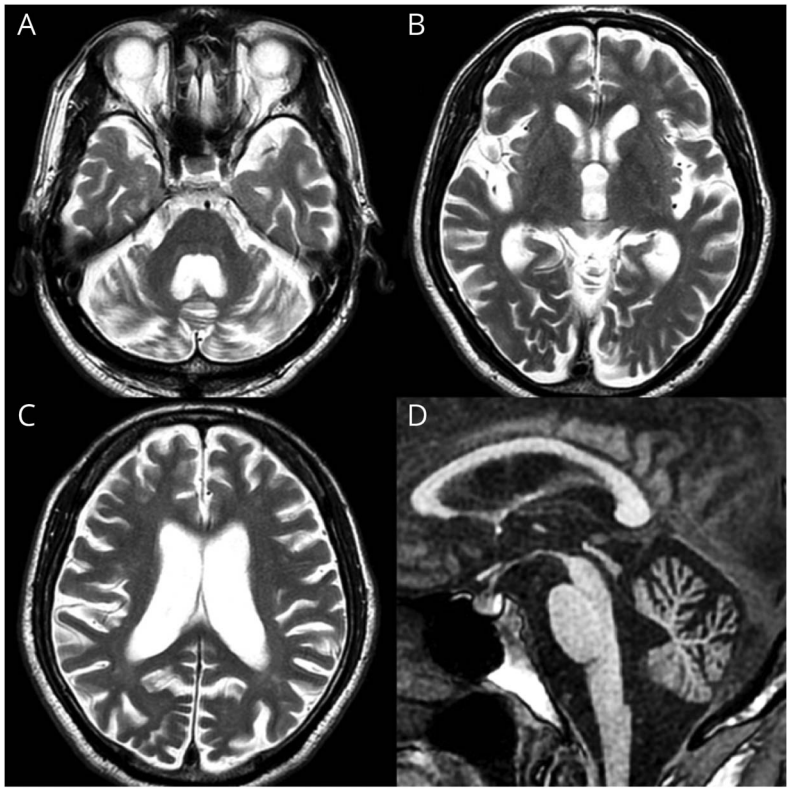
In the current case, the patient presented with generalized chorea, cerebellar ataxia, and mild cognitive impairment. The absence of deep tendon reflexes in the lower extremities could be related to diabetic neuropathy. The insidious onset and slow progression suggested that the disease was degenerative. Although the most common cause of chronic progressive chorea in adults is Huntington disease, cerebellar ataxia is unusual in patients with adult-onset Huntington disease and suggests an alternative diagnosis, such as spinocerebellar ataxia (SCA) (SCA1, 2, 3, 7, 8, 12, 17, and 48), dentatorubral-pallidoluysian atrophy (DRPLA), neuroacanthocytosis, Friedreich ataxia, Wilson disease, or mitochondrial disease (Table).[2,3] Nutritional deficiencies (vitamin B1 or B12) and infectious etiologies, such as syphilis and HIV, may present with similar manifestations. Although paraneoplastic syndrome may also present with a similar constellation of symptoms/signs, the insidious onset and slow progression over 16 years made these disorders less likely. Routine blood tests, including a complete blood count, and tests to assess liver function, renal profile, electrolytes, thyroid function, HIV status, and presence of syphilis were unremarkable. The patient's levels of vitamin B1, vitamin B12, serum ceruloplasmin, and creatine kinase were normal. Acanthocytes were not detected in his peripheral blood smears. His HbA1c was 6.8%, and his blood glucose was 147 mg/dL. Nerve conduction studies revealed sensory axonal polyneuropathy. Brain MRI

Table Differential Diagnoses for Adult-Onset Chorea and Cerebellar Ataxia of a Degenerative Nature

Differential diagnosis	Age at onset, y	Inheritance	Clinical features
SCA1	20–50	AD	Pyramidal signs
SCA2	20–50	AD	Pyramidal signs Parkinsonism
SCA3	5–70	AD	Bulging eyes Progressive external ophthalmoplegia Pyramidal signs Dystonic-rigid extrapyramidal signs Peripheral neuropathy
SCA7	10–30	AD	Retinal dystrophy
SCA8	20–40	AD	Drown-out slowness of speech
SCA12	30–50	AD	Action tremor
SCA17	20–50	AD	Cognitive and psychiatric changes Parkinsonism
SCA48	30–50	AD	Cognitive and psychiatric changes
DRPLA	5–70	AD	Seizures Cognitive and psychiatric changes
Chorea-acanthocytosis	20–40	AR	Self-injurious orofacial dyskinesia Cognitive and psychiatric changes
Friedreich ataxia	Before 25	AR	Peripheral neuropathy Cardiomyopathy Scoliosis Foot deformities
Wilson disease	6–50	AR	Cognitive and psychiatric changes Dystonia Kayser-Fleischer rings Liver disease
Aceruloplasminemia	30–70	AR	Retinal degeneration Diabetes mellitus
McLeod neuroacanthocytosis syndrome	Before 40	X-linked	Sensorimotor axonopathy Cardiomyopathy
Mitochondrial disease	Before 70	Maternal	Myopathy Cognitive and psychiatric changes Hearing loss Short stature Peripheral neuropathy

Abbreviations: AD = autosomal dominant; AR = autosomal recessive; DRPLA = dentatorubral-pallidoluysian atrophy; SCA = spinocerebellar ataxia.

Figure 1 Brain MRI



(A–C) Axial T2-weighted images and (D) sagittal T1-weighted image. Brain MRI shows severe cerebellar atrophy (A, D) and diffuse atrophy in the brainstem and cerebrum (B, C).

demonstrated prominent atrophy in the cerebellum, with diffuse atrophy in the brainstem and cerebrum (Figure 1). Ataxia panel testing for diagnoses within the SCA group, including SCA1, 2, 3, 6, 7, 8, 12, 17, and 31, and DRPLA was unremarkable.

Questions for Consideration:

1. What additional historic patient details could be important to obtain?
2. What further physical examinations should be performed?

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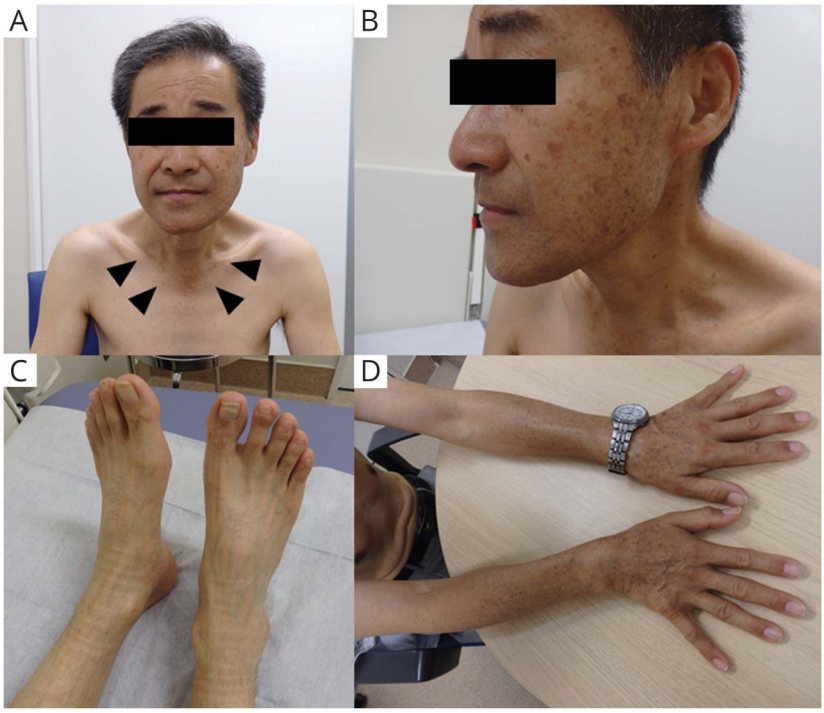
Section 3

Nutritional deficiencies, syphilis, HIV, Wilson disease, neuroacanthocytosis, SCAs (1, 2, 3, 7, 8, and 17), and DRPLA were excluded based on unsupportive laboratory, brain MRI, and genetic analysis results. However, the differential diagnosis was broad and included mitochondrial disease, rare SCAs (12 and 48), Friedreich ataxia, and rare genetic disorders that usually develop in childhood, such as xeroderma pigmentosum (XP).[2,3] Additional history was taken regarding sun sensitivity. The patient acknowledged photosensitivity with persistent erythema after limited sun exposure from childhood, although he did not recognize this symptom as a component of a disease. Skin examination revealed the freckling of sun-exposed regions (face, V area of the neck, forearms, and dorsal surface of the hands) (Figure 2). Referral to dermatology revealed basal cell carcinoma of the forehead, which was excised.

Question for Consideration:

1. What additional testing could confirm the diagnosis?

Figure 2 Photographs



Face (A, B), legs (C), and arms (D) photographs of the patient demonstrate freckling in the photo-exposed areas (arrowheads) (A, B, D). Note the clear demarcation with the zones usually protected by clothes (A, C, D).

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Section 4

DNA repair ability was assessed by measuring unscheduled DNA synthesis after irradiation with ultraviolet radiation C (UVC) using skin fibroblasts cultured from the patient. It was found to be decreased to 18% of normal cells. Based on the symptoms of acute and chronic photosensitivity and the result of the DNA repair test, a diagnosis of XP was made.[4] The genetic complementation group of XP was determined to be XP group F (XPF) based on the host cell reactivation assay, where the UV sensitivity of cells was restored only after the transfection of plasmid-containing XPF cDNA but with no other XP complementation group cDNAs. Next-generation sequencing revealed 3 missense variants of the *ERCC4* gene. Among the detected variants, c.2395C>T [p.Arg799Trp] has been reported as a pathogenic variant in previous studies of patients with XPF.[5-8] Computational predictions were made regarding the effects of the 2 remaining variants of uncertain significance (VUS) on the protein structure. The gene c.2413T>C [p.Ser805Pro] variant has not been reported in large population cohorts. Several in silico analyses, including polymorphism phenotyping V2 (PolyPhen-2), sorting intolerant from tolerant (SIFT), and Protein Variation Effect Analyzer (PROVEAN), suggest that this variant is benign, damaging, and deleterious, respectively. The gene c.2734G>A [p.Gly912Arg] is present in large population cohorts at a very low frequency. Therefore, its presence through several in silico analyses, including PolyPhen-2, SIFT, and PROVEAN, suggests that this variant is possibly damaging (PolyPhen-2 and SIFT) or neutral (PROVEAN). Based on the clinical and genetic features, we strongly speculate that XPF is caused by compound heterozygous variants of the *ERCC4* gene, the c.2395C>T gene, and either of these 2 VUS.

Discussion

XP is an autosomal recessive hereditary disorder of DNA repair primarily characterized by photosensitivity and predisposition to skin cancers. XP is classified into 7 complementation groups (A–G) and 1 variant form (XP-V). Although the variant form is associated with defects in translesion synthesis, the 7 complementation groups are associated with defects in nucleotide excision repair.[9] Progressive neurologic manifestations, including cognitive impairment, cerebellar ataxia, neuropathy, choreoathetoid involuntary movements, and sensorineural deafness, occur in about one-quarter of patients with XP in Western countries and in more than half of Japanese patients with XP.[4,10,11] In this case, cerebellar ataxia, chorea, and mild cognitive impairment were observed as neurologic manifestations of XP. The absent deep reflexes in the lower limbs and sensory axonal neuropathy were consistent with the diagnosis of diabetic polyneuropathy and/or polyneuropathy associated with XP.

Neurologic symptoms are primarily associated with XP group A (XPA) and group D (XPD) but have also been reported in patients with XP group B, XPF, and group G (XPG).[9,11,12] XPA, which exhibits the lowest DNA repair ability, is the most commonly affected complementation group and manifests the most severe neurologic symptoms, which develop in childhood.[9] Typically, the first neurologic symptoms of cognitive impairment appear before 8 years of age.[10] The next neurologic symptoms are generally cerebellar symptoms, which usually occur between 4 and 16 years of age, and, in conjunction with the neuropathy that appears later, cause gait disturbance.[9,10] Aspiration pneumonia, laryngeal dystonia, and vocal cord paralysis lead to death before the age of 40 years.[4,10] Homozygotes of the IVS3-1G>C variation in the *XPA* gene, known as the founder variation, account for more than 85% of the Japanese patients who have XPA and severe neurologic abnormalities.[4,9] In Japanese patients with XPA, motor and speech functions were reported to decline after the age of 6 years because of neurologic manifestations and length-dependent polyneuropathy beginning in the first decade.[9,13] On the other hand, cases of XPA mild form, XPF, and XPG, in which neurologic symptoms develop in adulthood, have been reported.[6-8,12,14,15] In these cases of adult-onset neurologic symptoms, cerebellar ataxia, chorea, and cognitive dysfunction were the core symptoms and were accompanied by various combinations of hearing loss, neuropathy, and pyramidal tract signs.[6-8,12,14,15] Therefore, XP can be a differential diagnosis for adult-onset cerebellar ataxia and chorea.

XP may be undiagnosed and latent in patients with spinocerebellar degeneration of unknown etiology. In the current case, the skin manifestations were mild and were not recognized by the patient as disease symptoms. Exome sequencing in patients with suspected hereditary SCA has revealed *ERCC4* variants that have been known to cause XPF.[5,7] In these patients with identified *ERCC4* variants, skin manifestations were not considered as symptoms of a disease until genetic diagnosis, as in the current case. Timely diagnosis of XP is important for the initiation of education regarding sun protection and for early detection and excision of malignant skin tumors.[4] The available pharmacologic therapy for neurologic manifestations of XP is limited to symptomatic treatment. Because oxidative stress and mitochondrial dysfunction are presumed to be pathologic mechanisms, antioxidant therapies such as coenzyme Q_{10} supplementation have been investigated as a possible pharmacologic approach.[16] In patients with cerebellar ataxia, chorea, and cognitive dysfunction of unknown etiology, clinicians should examine the history of photosensitivity and carefully assess the skin, keeping XP in mind as a differential diagnosis.

Study Funding

This research was supported by AMED (grant no. JP20ek0109450h0001 to C.N. and Y.T. and grant no. JP20ek0109488 to C.N.) and a grant for research on intractable diseases from the Health and Labor Science, Japan (grant no. 20FC1043 to C.N.).

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* March 15, 2022. Accepted in final form June 21, 2022. Submitted and externally peer reviewed. The handling editor was Roy Strowd III, MD, MEd, MS.

Appendix Authors

Name	Location	Contribution
Atsuhiko Sugiyama, MD, PhD	Department of Neurology, Graduate School of Medicine, Chiba University, Japan	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and study concept or design
Chikako Nishigori, MD, PhD	Division of Dermatology, Department of Internal Related, Kobe University, Graduate School of Medicine, Japan	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Mariko Tsujimoto, MD, PhD	Division of Dermatology, Department of Internal Related, Kobe University, Graduate School of Medicine, Japan	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Yaei Togawa, MD, PhD	Department of Dermatology, Graduate School of Medicine, Chiba University, Japan	Drafting/revision of the manuscript for content, including medical writing for content
Satoshi Kuwabara, MD, PhD	Department of Neurology, Graduate School of Medicine, Chiba University, Japan	Drafting/revision of the manuscript for content, including medical writing for content

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Neurology 2022;99;618-624 Published Online before print August 2, 2022
DOI 10.1212/WNL.0000000000201065