



Quantitative analysis of brain atrophy in patients with xeroderma pigmentosum group A carrying the founder mutation in Japan



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ABSTRACT

Introduction: Xeroderma pigmentosum (XP) is an inherited congenital disease presenting with dermatological and neurological manifestations. In Japan, XP complementation group A (XP-A) is most frequently observed in eight clinical subtypes, and the homozygous founder mutation, IVS3-1G > C in *XPA*, suffer from severe manifestations including progressive brain atrophy since childhood. In this study, we used magnetic resonance imaging (MRI) and applied volumetric analysis to elucidate the start and the progression of the brain atrophy in these patients.

Material and methods: Twelve Japanese patients with XP-A carrying the founder mutation and seven controls were included. MRI was performed for each patient once or more. Three-dimensional T1 weighted images were segmented to gray matter, white matter, and cerebrospinal fluid, and each volume was calculated.

Results: Conventional MRI demonstrated progressive whole brain atrophy in patients with XP-A. Moreover, volumetric analysis showed that reductions of total gray matter volumes (GMV) and total brain volumes (TBV) started at the age of five. The slope of reduction was similar in all cases. The GMV and TBV values in controls were higher than those in XP-A cases after the age of five.

Conclusions: This is the first quantitative report presenting with the progression of brain atrophy in patients with XP-A. It is revealed that the brain atrophy started from early childhood in Japanese patients with XP-A carrying the homozygous founder mutation.

1. Introduction

Xeroderma pigmentosum (XP) is a hereditary autosomal recessive disease, presenting with pigmented freckles and an increased risk of skin cancer in sun-exposed body sites and have of the patients display exaggerated sunburn upon minimum sun exposure. XP is classified into eight clinical subtypes, consisting of 7 nucleotide excision repair deficient groups, namely groups A–G and a variant type; furthermore, patients with XP group A, B, D, F and G were observed to have neurological manifestations [1–4]. In Japan, XP group A (XP-A) is most frequently observed, and patients with homozygous mutation of IVS3-1 G > C in the *XPA* gene, known as the founder mutation, suffer from severe neurological and dermatological abnormalities [4–6].

The pathogenesis of neuronal injury in patients with XP is still unclear, and no definitive treatment is available. Most patients with XP-A

follow a similar clinical course of gradual deterioration that begins in childhood and ends in being bedridden when they reach adulthood [5,7,8]. In our clinical experience, most of these severely affected patients were almost always homozygote of the founder mutation.

While brain atrophy is apparent from childhood, quantitative analysis in neuroimaging study of XPA has not been conducted yet. Some studies including the qualitative assessment of brain computed tomography or magnetic resonance imaging (MRI) in patients with XP were reported [7,9]. We have previously documented the clinical symptoms and degeneration of the central nervous system using diffusion tensor imaging or MR spectroscopy with no disease-specific findings in pediatric patients with XP-A [10].

In this study, we analyzed MRI volumetry to elucidate the start and progression of brain atrophy in patients with XP-A carrying the founder mutation in Japan. This is the first quantitative report presenting with the progression of brain atrophy in patients with XP-A.

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Table 1
Characteristics of XP-A patients and controls.

XP-A patients	Sex	Age at MRI						
Pt.1	M	1 y2 m	2 y3 m	3 y5 m	4 y5 m	5 y6 m	6 y11 m	
Pt.2	M	1 y8 m	4 y3 m					
Pt.3	F	3 y1 m						
Pt.4	F	3 y11 m	5 y2 m	5 y11 m				
Pt.5	F	6 y4 m	7 y4 m	8 y6 m	9 y6 m	10 y7 m	13 y4 m	
Pt.6	M	6 y7 m	8 y2 m	9 y7 m	11 y1 m	12 y3 m		
Pt.7	M	7 y11 m	11 y3 m					
Pt.8	F	8 y4 m	9 y6 m					
Pt.9	F	8 y7 m						
Pt.10	F	9 y11 m	10 y11 m	11 y11 m	12 y11 m	13 y11 m	15 y1 m	16 y1 m
Pt.11	M	18 y2 m	19 y9 m	21 y6 m				
Pt.12	F	20 y5 m						

Controls	Sex	Age at MRI
short stature	F	3 y1 m
ASD	M	5 y6 m
Tourette	F	8 y11 m
epilepsy	F	11 y8 m
PKC	M	14 y8 m
XP-D	F	14 y9 m
GBS	M	17 y0 m

XP-A, xeroderma pigmentosum group A; MRI, magnetic resonance imaging; M, male; F, female; y, years old; m, months old; ASD, autism spectrum disorder; PKC, paroxysmal kinesigenic choreoathetosis; XP-D, xeroderma pigmentosum group D; GBS Guillain-Barre syndrome.

2. Material and methods

2.1. Subjects

Twelve Japanese patients with XP-A were included in this study. All patients were genetically determined as harboring IVS3-1 G > C in the XPA gene by direct sequencing or polymerase chain reaction-restriction fragment length polymorphism using the restriction enzyme *AlwNI* as previously described [5]. MRI was performed for each patient according to protocol described below. Some patients were followed up for several years to observe a change with aging (Table 1). We administered sedative agents to patients unable to be at rest during the acquisition of MRI. The following seven individuals with no manifestations of brain atrophy were also obtained; patients with short stature, autism spectrum disorder (ASD), Tourette syndrome, epilepsy, XP group D (XP-D), paroxysmal kinesigenic choreoathetosis (PKC), and Guillain-Barre syndrome. XP-D often manifests no or subtle neurological symptom in Japan, and our patient has reported as non-neurological phenotype [11,12].

2.2. Magnetic resonance imaging

T1-weighted images (T1WI) (TE = 3.3 ms, TR = 7.2 ms, flip angle = 8°, FOV = 256 × 256 mm², matrix = 512 × 512, ST = 0.8 mm) were obtained using a 3-Tesla MRI (Phillips Medical Systems, Eindhoven, Netherlands). T1WI was acquired with a 0.8 mm slice thickness for three dimensional (3D) reconstructions. Images were analyzed using Statistical Parametric Mapping software (SPM12, Welcome Trust Centre for Neuroimaging, University College London, UK) working on MATLAB software (R2015a, The Mathworks Inc., Natick, MA, USA). 3D Images were segmented to gray matter, white matter, and cerebrospinal fluid using the

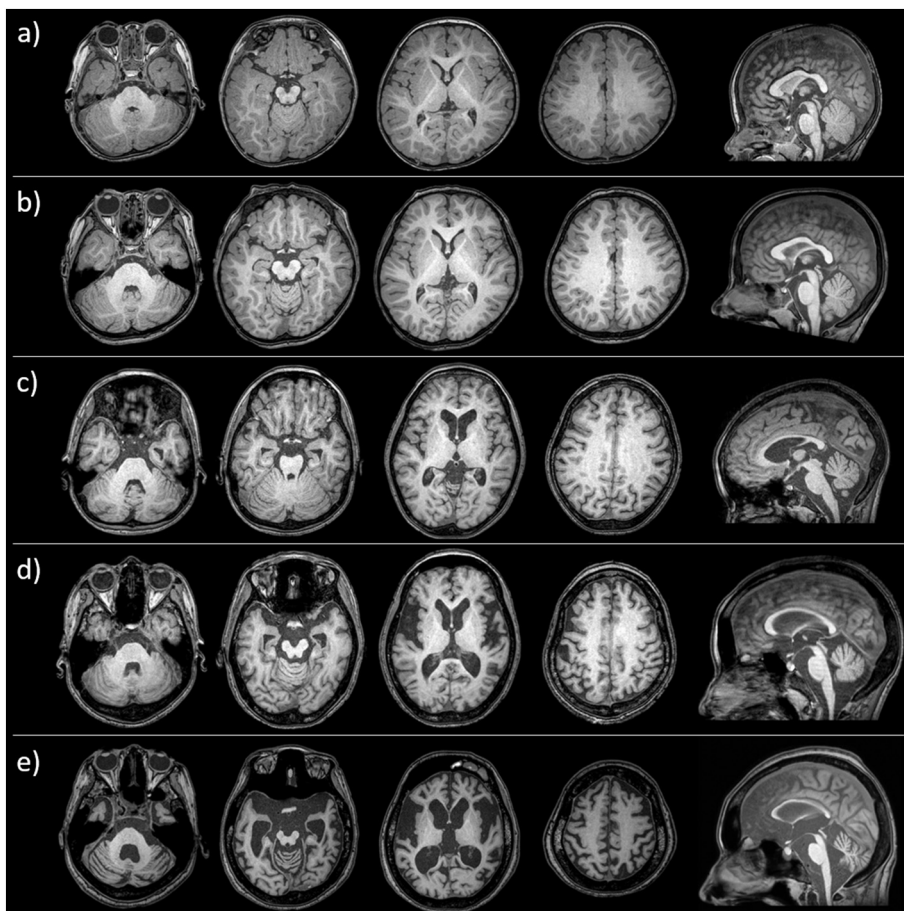


Fig. 1. Axial and sagittal views on T1 weighted images in patients with XP-A
a–b): XP-A Pt.1 at the age of 1 y.o. (a) and 5 y.o. (b)
c–d): XP-A Pt.10 at the age of 10 y.o. (c) and 15 y.o. (d)
e): XP-A Pt.12 at the age of 20 y.o.

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