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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.

Highlights

Xeroderma pigmentosum group A (XP-A) manifests severe neurological deteriorations.

In Japan, most patients are carrying founder mutation in *XPA* gene.

We revealed the brain atrophy started from early childhood in patients with XP-A using quantitative methods of magnetic resonance imaging.

Keywords

xeroderma pigmentosum, XP-A, brain atrophy, gray matter volume, 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.

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 *Alw*NI 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). 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 manifest no or subtle neurological symptom in Japan, and our patient has reported as non-neurological phenotype [11, 12].

Table. Characteristics of XP-A patients and controls.

XP-A patients	sex	age at MRI						
Pt.1	M	1y2m	2y3m	3y5m	4y5m	5y6m	6y11m	
Pt.2	M	1y8m	4y3m					
Pt.3	F	3y1m						
Pt.4	F	3y11m	5y2m	5y11m				
Pt.5	F	6y4m	7y4m	8y6m	9y6m	10y7m	13y4m	
Pt.6	M	6y7m	8y2m	9y7m	11y1m	12y3m		
Pt.7	M	7y11m	11y3m					
Pt.8	F	8y4m	9y6m					
Pt.9	F	8y7m						
Pt.10	F	9y11m	10y11m	11y11m	12y11m	13y11m	15y1m	16y1m
Pt.11	M	18y2m	19y9m	21y6m				
Pt.12	F	20y5m						

Controls	sex	age at MRI
short stature	F	3y1m
ASD	M	5y6m
Tourette	F	8y11m
epilepsy	F	11y8m
PKC	M	14y8m
XP-D	F	14y9m
GBS	M	17y0m

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 pigmentsum group D; GBS Guillain-Barre syndrome

2.2 Magnetic Resonance Imaging

T1-weighted images (T1WI) (TE = 3.3 ms, TR = 7.2 ms, flip angle = 8°, FOV = 256 × 256 mm^2, matrix = 512 × 512, ST = 0.8 mm) were obtained using a 3-Tesla MRI (Phillips Medical Systems, Eindhoven, Netherlands). T1WI was acquired with a 0.8mm 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 segmentation protocol in SPM12. The total gray matter volume (GMV), white matter volume (WMV), and cerebrospinal fluid volume (CSF) were calculated by the MATLAB get_totals script (http://www.cs.ucl.ac.uk/staff/g.ridgway/vbm/) implemented for SPM. Furthermore, the total brain volume (TBV, sum of GMV and WMV) was calculated [13].

2.3 Informed Consent

In accordance with the ethical guidelines of the Declaration of Helsinki, written informed consent was obtained from guardians of all XP-A patients and controls under the protocols approved by the Institutional Review Board of Kobe University Graduate School of Medicine, Hyogo, Japan.

3. Results

3.1 Conventional sequences

Conventional MRI demonstrated progressive whole brain atrophy in patients with XP-A (Fig. 1). In addition, paranasal sinuses expanded in older patients. Although microcephaly was observed, brain structures were not disproportional to each other.

3.2 Volumetric analysis

Brain volumetric analysis demonstrated the decrease of brain volumes in XP-A patients after the age of five (Fig. 2). Although the GMV or TBV values were different among individuals, the slope of reduction was similar in all cases. Under the age of five, GMV and TBV increased in XP-A Pt.1. Controls after the age of five had higher values of GMV and TBV than those in XP-A cases while no difference was seen at the age of three. There was no tendency between sexes.

4. Discussion

The neurodegeneration in severe XP-A phenotype spreads to almost all areas of the nervous system; the central and the peripheral, the motor and the sensory, and the pyramidal, the extra-pyramidal, and the cerebellar tract [7, 10]. The onset of neurological manifestations or intrinsic neurodegeneration is still controversial. While mental retardation and delayed motor development mask the neurological problems [9], patients initially can walk unaided before gradually losing that function during childhood. In the present study, we aimed to determine the onset and progression of deterioration by measuring brain volumes.

Here we showed that quantitative GMV and TBV data in patients with XP-A against controls without brain atrophy. According to studies of healthy individuals [14, 15], GMV increased rapidly from early to later (6–9 years) childhood, thereafter, GMV increased more slowly and reached a plateau in adolescence. TBV increased similarly. In comparison, our results indicated that GMV and TBV in XP-A decreased rapidly after the age of five, while no difference was seen at the age of three between XP-A patients and a control. Anttinen et al. reported that neurological deterioration starts at the age of eight in patients with XP-A [7], and we also showed that patients exhibited neurological dysfunction, such as cerebellar ataxia, at the age of six [10]. We speculate that gray matter atrophy antedate these clinical observations.

Surprisingly, the slope of reduction of GMV and TBV was constant and similar in all examined patients with XP-A. To date, there is no biomarker for neurological disorders in XP as well as no treatment ameliorating for neurological symptoms. If new therapies are developed in the future, GMV would be a useful biomarker for therapeutic effects.

5. Conclusions

Our study demonstrated that the progression of brain atrophy started from early childhood before neurological manifestations were revealed, in patients with XP-A carrying the founder mutation in Japan. While the underlying pathology of the neurodegeneration in XP has yet to be elucidated, accumulating evidence in the clinical analysis promise a better understanding of not only XP but also other neurodegenerative diseases.

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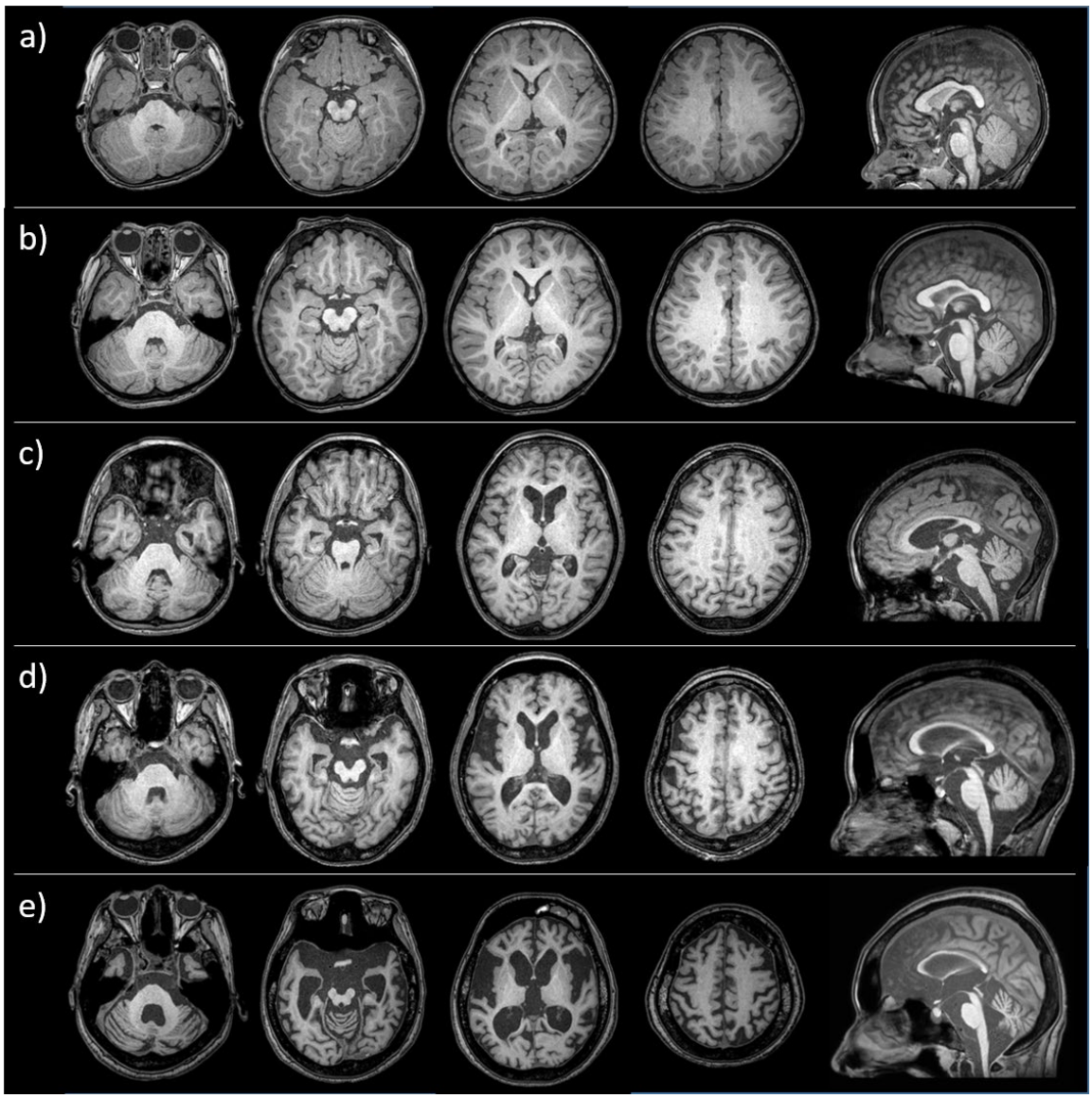
Conflict of interests

The authors have declared no conflicting interests.

Figure 1.



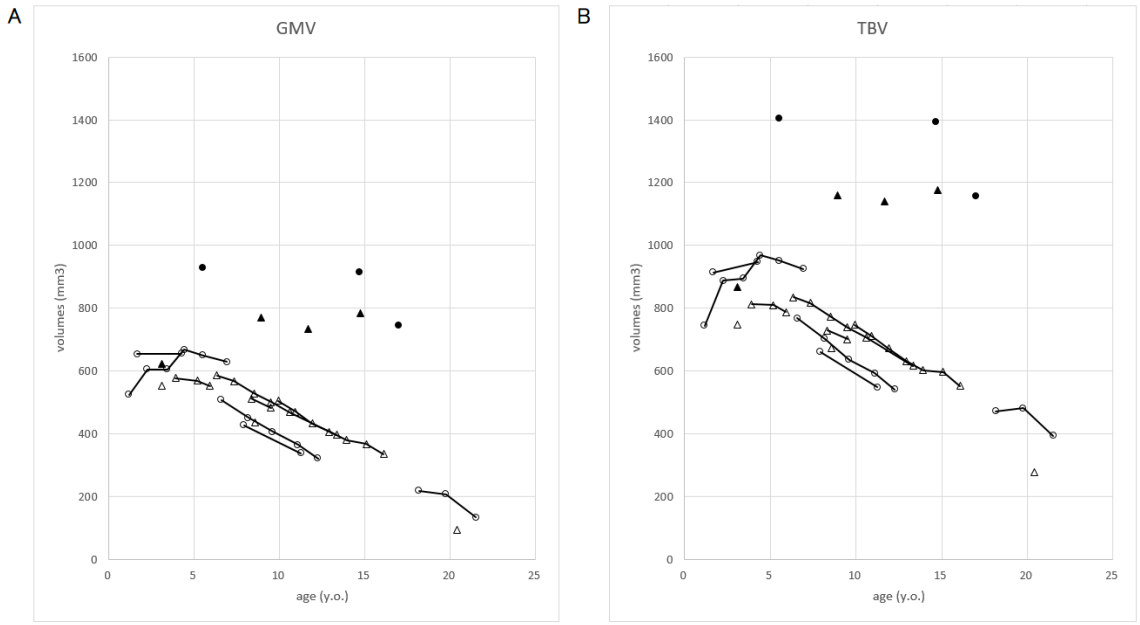
Axial and sagittal views on T1 weighted images in patients with XP-A

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.

Figure 2.



A: Gray matter volumes (GMV) and **B**: Total brain volumes (TBV).

They are plotted against the age of patients. The values of the same patient are connected by the line.

open circle, male xeroderma pigmentosum group A (XP-A); open triangle, female XP-A; filled circle, male control; filled triangle, female control

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