• Clinical Research •

Temporal retinal thinning might be an early diagnostic indicator in male pediatric X-linked Alport syndrome

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Abstract

● **AIM:** To evaluate temporal retinal thinning changes in retinal layers using spectral-domain optical coherence tomography (SD-OCT) in pediatric X-linked Alport syndrome (XLAS) patients.

● **METHODS:** A retrospective case-control study. SD-OCT scans of pediatric patients diagnosed with XLAS and age- and sex-matched healthy control participants were reviewed. Automated segmentation of SD-OCT scans was induced to analyze the retinal thickness (RT) of different layers. The temporal thinning index (TTI) was calculated for each layer and compared between the patients and the control group.

● **RESULTS:** Forty-three pediatric XLAS patients and 60 healthy controls were included. Temporal retinal thinning was present in 33 patients (76.74%), while 28 patients (65.11%) had severe pathological temporal retinal thinning and 5 patients (11.63%) had moderate thinning. The temporal inner sector RT (P<0.0001), the temporal outer sector RT (P<0.0001), and the nasal outer sector RT (P=0.0211) were significantly thinner in the XLAS male patients. The TTI of the total retina was significantly higher in the XLAS group than in the control group (P<0.0001). The TTI of the inner retina layers (P<0.0001), ganglion cell layer (P<0.0001), inner plexiform layer (P<0.0001), inner nuclear layer (P<0.0001), and outer nuclear layer (P<0.0001) were significantly higher in the XLAS group. The central RT of the XLAS group was significantly thinner than that of the control group (P<0.0001).

● **CONCLUSION:** Temporal retinal thinning appears early in XLAS patients, especially in male patients. The thinning is mainly caused by structural abnormalities of the inner retina. This suggests that temporal retinal thinning could be helpful for the early diagnosis and follow-up of XLAS with noninvasive SD-OCT examination.

● **KEYWORDS:** Alport syndrome; retinal thickness; spectral domain optical coherence tomography; segmentation

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INTRODUCTION

Alport syndrome (AS) is a hereditary glomerular disease characterized by hematuria and progressive renal failure. The syndrome is usually associated with sensorineural hearing loss and distinct ocular abnormalities[1], and it is estimated to affect 1 in 5000-10 000 individuals[1]. AS is caused by mutations in the *COL4A3*, *COL4A4*, and *COL4A5* genes, which encode the α3, α4, and α5 chains of collagen type IV[2-3]. Approximately 85% of affected patients show an X-linked dominant inheritance form caused by mutations in the *COL4A5* gene[4-5].

Ocular abnormalities are common in AS patients, including corneal opacities, anterior lenticonus, and dot-and-fleck retinopathy[6-8]. In recent years, researchers from different groups have reported that temporal retinal thinning is a frequently detected ophthalmic feature in AS[6,9-11]. The occurrence of temporal retinal thinning is more common than other ocular abnormalities and is independent of other ocular features in AS patients. Ahmed *et al*[12] generated a temporal thinning index (TTI) to analyze temporal retinal thinning in X-linked Alport syndrome (XLAS) patients. Their reported data revealed that in XLAS patients, 70% of the patients had severe thinning, and 11% of them had moderate thinning[12]. Most studies measured total retinal thickness to calculate the extent of retinal thinning, and which retinal layer changed most was not addressed. Therefore, the characteristics of retinal thinning need to be elucidated. Previous studies on

temporal retinal thinning in AS have been conducted almost all in adult cohorts, and little is known about pediatric AS patients. Recently, researchers have demonstrated that retinal temporal thinning is diagnostic for XLAS in men[13-14]. Since the frequency and severity of typical ocular anomalies increase with age[8], temporal retinal thinning is more sensitive than typical ocular changes. Thus, in this study, we analyzed temporal retinal thinning with spectral domain optical coherence tomography (SD-OCT) and measured the retinal thickness of different retinal layers to investigate temporal retinal thinning changes in XLAS patients. We investigated temporal thinning in pediatric patients to study this feature at an early stage of the disease.

SUBJECTS AND METHODS

Ethical Approval The study follows the tenets of the Declaration of Helsinki. The study was approved by the Institutional Review Board of Peking University First Hospital, Beijing, China (ID: 2017-1409). All patients' parents gave informed consent for data collection and analysis.

Participants We retrospectively reviewed the SD-OCT data and medical records of XLAS patients aged under 18y who received ophthalmic examination from January 2017 to September 2019 at Peking University First Hospital. All patients received genetic testing with Sanger sequencing or targeted whole exome sequencing. All the patients were confirmed to have a pathogenic variant in the *COL4A5* gene, and the diagnosis of XLAS was made at the Department of Pediatrics of Peking University First Hospital. Data evaluated included patient demographics, ocular history, slit-lamp and dilated fundus examination records. SD-OCT studies were reviewed. We recruited healthy children as a control group who received SD-OCT and ocular examination. The refractive error of these participants was between -5.75 DS to +2.75 DS. No anterior segment or fundus changes were identified in the control group children. The systemic medical history was unremarkable in the control group.

Spectral Domain Optical Coherence Tomography SD-OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany) was performed in a high-resolution mode on all patients to assess macular thickness changes. The macular cube volumetric scans were obtained centered at the fovea, including 49 B-scans and 15 automated real-time repetitions. Retinal layer segmentation was executed automatically using Spectralis OCT built-in software (Heidelberg Eye Version 1.10.2.0).

The auto segmentation software determined 11 different retinal boundaries (Figure 1): the inner limiting membrane (ILM), the boundaries between the retinal nerve fiber layer (RNFL) and the ganglion cell layer (GCL), between the GCL and the inner plexiform layer (IPL), between the IPL and the inner nuclear layer (INL), between the INL and the outer plexiform layer (OPL), between the OPL and the outer nuclear layer (ONL), the external limiting membrane (ELM), two photoreceptor layers (PR1/2), the retinal pigment epithelium (RPE), and Bruch's membrane (BM). Thickness of the following layers was automatically calculated: RNFL, GCL, IPL, INL, OPL, ONL, RPE, total retinal thickness (RT, comprising the ILM and BM), inner retinal layers (IRLs, comprising the ILM and the ELM), and outer retinal layers (ORLs, comprising the ELM and the BM).

All the images were reviewed by an ophthalmologist (Zhao L), who was masked to clinical information. Poor-quality images with a signal strength less than 20 dB, poor centration, or incorrect segmentation images were discarded.

The foveal center was automatically identified by the SD-OCT software, and it was used as the center of the Early Treatment of Diabetic Retinopathy Study (ETDRS) grid. The ETDRS grid was used to analyze the average thickness of the different layers. As described by Ahmed *et al*[12], the standard 6-mm macular OCT grid as defined by the ETDRS circle was labeled with 1-, 3-, and 6-mm-diameter circles centered at the fovea. The average of all measurements within the inner 1-mm circle was defined as central retinal thickness (CRT). The average retinal thickness in each of the nine macular sectors in the 6-mm diameter circle of each layer was evaluated automatically.

Temporal Thinning Index calculation According to Ahmed's formula[12], the TTI was calculated with the following formula:

$$TT1=\frac{(N1+N2)-(T1+T2)}{N1+N2}\times 100$$

N1 and N2 were the average thicknesses (μm) of the inner and outer nasal segments, respectively, and T1 and T2 were the average thicknesses (μm) of the inner and outer temporal segments, respectively (Figure 2). According to Ahmed's report[12], the TTI was subdivided into 3 categories based on the TTI mean value and SD value of the normal children in the control group. Normal physiological thinning was defined as a TTI<1 SD of the normal mean value, moderate pathological thinning was defined as a TTI 1-2 SDs above the normal mean value, and severe pathological thinning was defined as a TTI >2 SDs above the normal mean value.

As mentioned in Chen *et al*'s study[13], there was no difference in the TTI between the right eye and left eye, so the data of the right eyes were collected in our study. The TTI of the following layers was evaluated: RNFL, GCL, IPL, INL, OPL, ONL, RPE, RT, IRLs, and ORLs.

Statistical Analysis GraphPad Prism 9 (GraphPad Software, San Diego, USA) was used for statistical analyses. Baseline descriptive characteristics (age, sex) were compared between the healthy and XLAS groups using an unpaired Student's

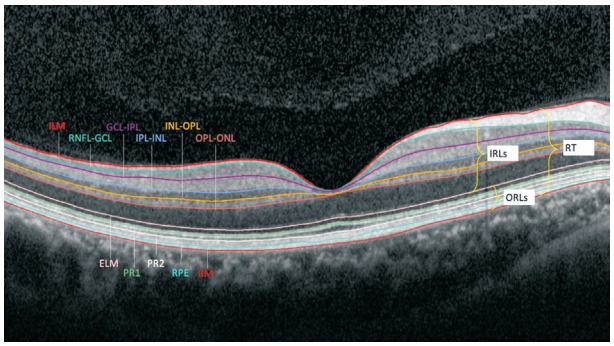

Figure 1 The automated segmentation diagram Heidelberg software segmented the retina into 11 different boundaries: the inner limiting membrane (ILM), the boundaries between the retinal nerve fiber layer and the ganglion cell layer (RNFL-GCL), the GCL and the inner plexiform layer (GCL-IPL), the IPL and the inner nuclear layer (IPL-INL), the INL and the outer plexiform layer (INL-OPL), the OPL and the outer nuclear layer (OPL-ONL), the external limiting membrane (ELM), two photoreceptor layers (PR1/2), the RPE, and Bruch's membrane (BM). Total retinal thickness (RT), inner retinal layers (IRLs), and outer retinal layers (ORLs).

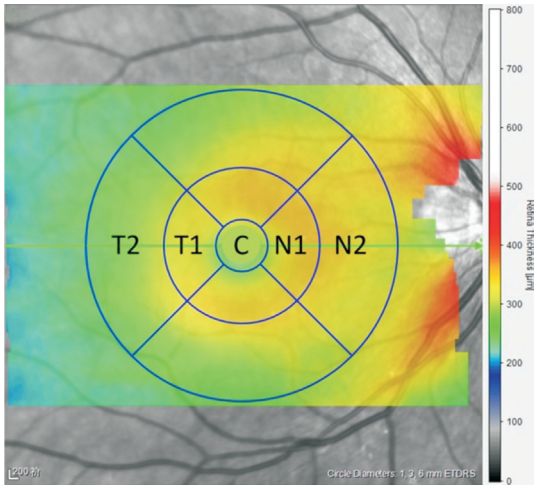

Figure 2 Retinal thickness map with ETDRS grid A retinal thickness map of the right eye. The 1-, 3-, and 6-mm diameter grid showing the areas of retina labeled with C (central retina), T1 (temporal inner sector), T2 (temporal outer sector), N1 (nasal inner sector), and N2 (nasal outer sector).

t-test for quantitative variables and Fisher's exact test for categorical variables. The CRT and TTI of different layers were compared between the groups, and a *P* value <0.05 was considered statistically significant. The relationship between TTI and the age of XLAS patients was determined using Spearman's *r* correlation coefficient.

RESULTS

In this retrospective study, 43 patients diagnosed with XLAS were included. Thirty-five (81.40%) of the patients were male. The mean age of the patients was 10.07±2.95 (range 4-15)y when they received the SD-OCT examination. Sixty ametropia patients were included as control subjects. The mean age of the control group was 9.28±2.65 (range 5-16)y. Demographic data of the patients are shown in Table 1. There were no significant differences in age or sex between the two groups.

Table 1 Demographic characteristics of the participants

mean±SD (range)

Parameters	XLAS	Control	*P*
Male, *n* (%)	35 (81.40%)	43 (71.67%)	0.26
Age, y	10.74±2.58 (6-15)	9.81±2.70 (5-16)	0.14
Female, *n* (%)	8 (18.60%)	17 (28.33%)	
Age, y	7.13±2.75 (4-12)	8.18±2.22 (5-13)	0.32

XLAS: X-linked Alport syndrome.

Table 2 Total retinal thickness measured by SD-OCT

mean±SD, μm

Parameters	T2	T1	N1	N2
Male				
XLAS	264.8±16.18	300.6±23.63	333.6±29.45	309.0±18.18
Control	287.2±12.49	326.3±12.60	338.5±13.60	318.0±13.69
P	<0.0001[c]	<0.0001[c]	0.3690	0.0211[a]
Female				
XLAS	280.1±14.28	319.0±14.60	335.4±19.62	319.3±18.69
Control	283.8±14.23	323.3±12.15	336.7±13.52	315.9±16.05
P	0.5458	0.4433	0.8402	0.6433

T2: Temporal outer sector; T1: Temporal inner sector; N1: Nasal inner sector; N2: Nasal outer sector; XLAS: X-linked Alport syndrome. [a]*P*<0.05, [b]*P*<0.01, [c]*P*<0.001.

Ocular abnormalities were found as below. Dot-and-fleck retinopathy was found in 8 patients (18.60%), and all of them were male. One male patient had pseudophakia due to lenticonus (2.33%). No corneal abnormality was found in our study. Visual acuity was recorded for the patients over 8 years old, and the best corrected visual acuity for all of them was 1.0. The total retinal thickness was shown in Table 2. Compared with the control group, the temporal inner sector retinal thickness (*P*<0.0001), the temporal outer sector retinal thickness (*P*<0.0001), and the nasal outer sector retinal thickness (*P*=0.0211) were significantly thinner in the XLAS male patients. There was no significant difference in retinal thickness between female XLAS patients and the control group. The TTI result was shown in Table 3. The TTI of the total retina (*P*<0.0001) was significantly higher in the XLAS group than in the control group. According to the criteria mentioned by Ahmed *et al*[12], based on the TTI mean value and SD value of the normal children in the control group, there was temporal retinal thinning in 33 patients (76.74%), while 28 patients (65.11%) had severe pathological temporal retinal thinning and 5 patients (11.63%) had moderate thinning.

With automated segmentation analysis, the TTI of the inner retina layers (*P*<0.0001), GCL (*P*<0.0001), IPL (*P*<0.0001), INL (*P*<0.0001), and ONL (*P*<0.0001) were significantly

higher in the XLAS group. There were no significant differences in the TTI in other layers. The CRT of the XLAS patients was 234.40±28.69 μm (range 168-294 μm) and 257.30±16.62 μm (range 225-293 μm) in the control group. The CRT of the XLAS group was significantly thinner than that of the control group (P<0.0001).

Ocular abnormalities were generally more prominent in male XLAS patients. In our patient group, severe temporal retinal thinning was 27 (77.14%) in male patients *vs* 1 (12.50%) in female patients, and the retinal thickness measured by SD-OCT was significantly different in the male group (Table 2). Thus, we further analyzed the TTI in different sexes. The results were shown in Tables 4 and 5.

In male patients, the TTI of the total retina (P<0.0001), inner retina layers (P<0.0001), GCL (P<0.0001), IPL (P<0.0001), INL (P<0.0001), and ONL (P=0.0012) were significantly higher in the XLAS group. Twenty-seven male patients (77.14%) had severe pathological temporal retinal thinning. All the 27 patients had severe pathological temporal retinal thinning in inner retina layer, while 24 of the male patients (68.57%) had severe temporal thinning in the INL layer. The CRT of the XLAS group (233.40±31.11 μm) was significantly thinner than that of the control group (258.90±17.11 μm; P<0.0001). Figure 3 is a representative SD-OCT result of an XLAS patient.

In female patients, the TTI of the total retina (P=0.0248) was significantly higher in the XLAS group, while the TTI of the inner retina layers (P=0.0669) and outer retina layers (P=0.1070) were not significantly different between the two groups. The CRT of the female XLAS patients (238.10±17.33 μm) was significantly thinner than that of the control group (254.10±15.54 μm; P=0.0285). Age was not correlated with retinal temporal thinning in either male patients (r=-0.1356, P=0.4372) or female patients (r=0.1537, P=0.7163).

DISCUSSION

Retinal temporal thinning detected with SD-OCT is demonstrated as a common ocular change in AS. In 2004, Usui *et al*[15] reported an AS patient with symmetrical reduced thickness of the temporal macular area in both eyes, while the visual function of the patient was normal. During the following years, some other researchers reported AS patients with focal zones of inner retinal thinning in the temporal quadrant[16-19]. In 2013, Ahmed *et al*[12] suggested using the TTI parameter to assess the degree of retinal temporal thinning in AS patients. The TTI parameter was then adopted by other study groups and became an important index for evaluating temporal retinal thinning in AS patients. We compared the retinal thickness in nasal and temporal sectors between XLAS patients and the control group. Since the range of variation of the retinal thickness was

Table 3 TTI of different layers mean±SD

Parameters	XLAS	Control	P
Total retina	11.22±3.37	6.71±1.41	<0.0001[c]
Inner retina	14.24±4.39	8.42±1.73	<0.0001[c]
Outer retina	1.78±1.65	137±1.41	0.1990
RNFL	47.51±6.19	47.80±4.96	0.7988
GCL	14.54±6.17	6.08±4.97	<0.0001[c]
IPL	6.04±6.62	-2.40±4.07	<0.0001[c]
INL	12.20±7.68	3.69±3.86	<0.0001[c]
OPL	2.49±10.13	3.09±11.72	0.7931
ONL	7.95±8.66	-0.30±9.35	<0.0001[c]
RPE	8.17±5.88	6.36±7.57	0.2012

RNFL: Retinal nerve fiber layer; GCL: Ganglion cell layer; IPL: Inner plexiform layer; INL: Inner nuclear layer; OPL: Outer plexiform layer; ONL: Outer nuclear layer; RPE: Retinal pigment epithelium; XLAS: X-linked Alport syndrome; TTI: Temporal thinning index. [c]P<0.001.

Table 4 TTI of different layers in male patients mean±SD

Parameters	XLAS	Control	P
Total retina	11.95±3.30	6.54±1.56	<0.0001[c]
Inner retina	15.22±4.26	8.16±1.89	<0.0001[c]
Outer retina	1.70±1.80	1.41±1.48	0.4589
RNFL	47.79±6.66	48.13±5.09	0.8097
GCL	16.09±5.50	5.51±5.15	<0.0001[c]
IPL	7.30±6.67	-2.86±4.19	<0.0001[c]
INL	13.87±7.43	2.83±3.78	<0.0001[c]
OPL	4.04±9.78	1.44±12.51	0.3344
ONL	8.02±9.24	0.38±9.75	0.0012[b]
RPE	7.32±6.09	7.42±7.35	0.9514

RNFL: Retinal nerve fiber layer; GCL: Ganglion cell layer; IPL: Inner plexiform layer; INL: Inner nuclear layer; OPL: Outer plexiform layer; ONL: Outer nuclear layer; RPE: Retinal pigment epithelium; XLAS: X-linked Alport syndrome; TTI: Temporal thinning index. [b]P<0.01, [c]P<0.001.

Table 5 TTI of different layers in female patients mean±SD

Parameters	XLAS	Control	P
Total retina	8.03±0.87	7.08±0.95	0.0248[a]
Inner retina	9.96±1.21	8.98±1.82	0.0669
Outer retina	2.13±0.65	1.30±1.31	0.1070
RNFL	46.28±3.55	47.14±4.76	0.6523
GCL	7.74±4.05	7.22±4.53	0.7842
IPL	0.52±2.01	-1.49±3.76	0.1701
INL	4.88±3.18	5.40±3.53	0.7233
OPL	-4.26±9.35	6.38±9.42	0.0136[a]
ONL	7.68±5.93	-1.64±8.59	0.0105[a]
RPE	11.90±2.83	4.26±7.77	0.0132[a]

RNFL: Retinal nerve fiber layer; GCL: Ganglion cell layer; IPL: Inner plexiform layer; INL: Inner nuclear layer; OPL: Outer plexiform layer, ONL: Outer nuclear layer; RPE: Retinal pigment epithelium; XLAS: X-linked Alport syndrome; TTI: Temporal thinning index. [a]P<0.05.

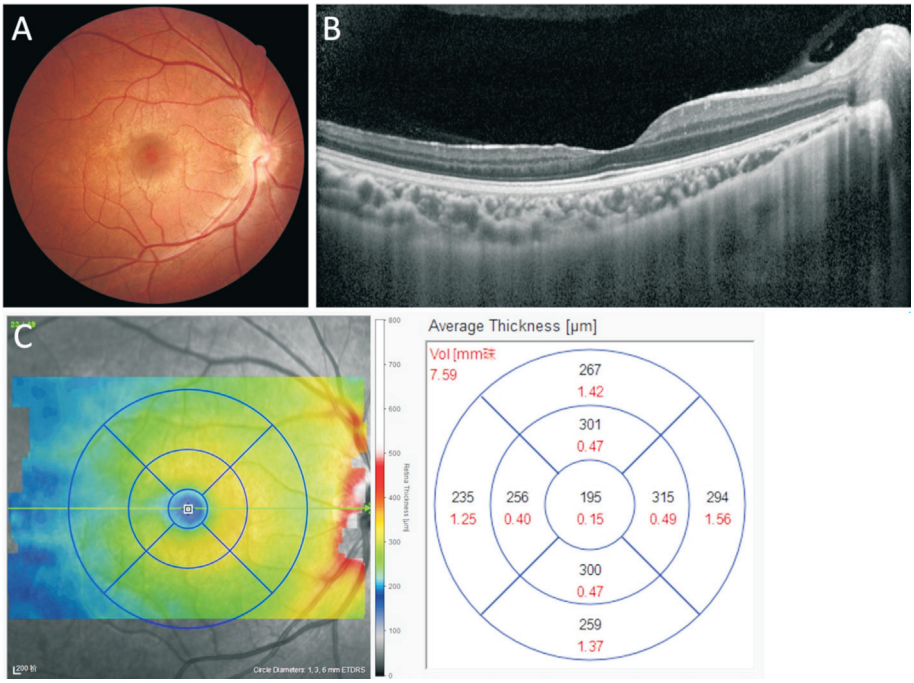

Figure 3 A representative fundus and SD-OCT scan image of an XLAS patient A 14-year-old boy was diagnosed with AS 6 years ago, and his bilateral corrected visual acuity was 1.0. Dot-and-fleck retinopathy could be seen as yellowish dots around the macula. His lens was normal. SD-OCT scans of his retina revealed temporal retinal thinning. A: The fundus photograph of the patient showed yellowish dots around his macula; B: The B-scan of the patient showing significant temporal retinal thinning; C: The retinal thickness map of the patient.

large in different papers[20-22], the TTI was useful to address the relative thinning of the temporal quadrant. Therefore, we use the TTI as our main result. It also made the results of our study comparable to previous reports by other investigators[12-13].

Temporal retinal thinning is more common than other AS ocular changes, *i.e.*, anterior lenticonus, the lozenge sign, or dot-and-fleck retinopathy. Among the XLAS patients included in Ahmed *et al*'s[12] study, 81% of the patients had moderate to severe thinning, while less than 20% eyes had other ocular findings[12]. Savige *et al*[23] reported that 89% male XLAS patients and 75% female XLAS patients had temporal retinal thinning. In our study, 33 (76.74%) patients had moderate to severe temporal retinal thinning, while dot-and-fleck retinopathy and lenticonus were found in only 18.60% and 2.33% patients, respectively. Since temporal retinal thinning is a sensitive and specific feature of AS, Chen *et al*[13] and Zhao *et al*[24] both have identified its diagnostic value in screening AS.

However, the pathogenesis of temporal retinal thinning is not fully understood. Previous studies suggested that thinning mainly affects the ILM and RNFL[23]. Some researchers assumed that the temporal thinning phenomenon in AS may be related to the postnatal development of the macula, tractional vitreoretinal forces, or aberrant Müller cell adhesion[12]. In our study, we used SD-OCT segmentation analysis to investigate the exact layer that changes most in AS. We included only XLAS pediatric patients to eliminate interference factors and observe the changes in the early stage of the disease.

We identified that temporal retinal thinning existed in XLAS patients at an early age. The youngest patient with temporal retinal thinning in our study was a 4-year-old girl whose TTI was 9.10. A 6-year-old boy in our patient group had severe temporal retinal thinning with a TTI of 11.27. Retinal thinning in male pediatric patients was more significant. With segmentation analysis, our results confirmed that the inner retinal structure change led to temporal retinal thinning, which was consistent with other researchers' reports[9,17,23]. The GCL, IPL and INL thinning were significant.

Some investigators speculated that the ILM played an important role in retinal thinning. The key pathologic change in AS is the abnormality of type IV collagen, which is also the main component of ILM. Savige *et al*[23] reported the ILM thinning in AS patient. On the other hand, in some patients who underwent the ILM peeling procedure, similar retinal structure changes were also noted in non-AS patients. Fukukita *et al*[25] found that the retina of patients undergoing vitrectomy with ILM peeling had similar changes to AS, and their inner retina thinned predominantly in the temporal area. Hisatomi *et al*[26] found similar changes after ILM peeling. Imamura *et al*[27] observed retinal thinning occurring mainly in the temporal sector in macular hole patients after vitrectomy with ILM peeling. The retinal structure changes after ILM peeling indicated that the ILM was crucial in normal retinal structural maintenance, and temporal retinal thinning was caused by the loss of ILM[25,27]. Savige *et al*[23] indicated that

since the ILM is a fusion of the foot processes of Müller cells, retinopathy may thus originate in Müller cells. However, the ultrastructural changes in these layers and cells still need further morphological studies for clarification.

Our results showed that the central retinal thickness was significantly thinner in XLAS patients than in the control group. Stanojcic *et al*[28] also reported foveal thinning in an AS patient. Usui *et al*[15] reported a case with bilateral symmetrical temporal retinal thinning while preserving the foveal thickness within the normal range. Most studies on temporal retinal thinning in AS did not assess CRT changes. The normal range of CRT in children measured with Spectralis SD-OCT was reported to be 214-301 μm[29-30]. In our research, the CRT of XLAS children was significantly thinner than that of the control group. Although all female patients' CRTs were within the normal range, some of the male patients' CRTs were thinner than the lower limit of the normal range. Whether CRT thinning develops with disease progression needs long-term observation.

In our study, we did not observe a decrease in visual acuity in the XLAS patients. Whether retinal temporal thinning affects patients' visual function is still debatable. Wong *et al*[9] tested visual function with microperimetry, and the results showed no definite decline in sensitivity corresponding to the areas of retinal thinning. Savige *et al*[6] demonstrated that retinal function was normal when there was thinning only. Borgman *et al*[14] reported an XLAS patient with temporal retinal thinning, and the mfERG test showed reduced signals of the temporal retina, which was correlated with the patient's temporal retinal thinning. In our study, we only recorded visual acuity in patients over 8 years old, and no other tests were performed to assess the visual function of the patients. More investigations are required to identify the problem.

The limitations of our research included that this study was a cross-sectional retrospective study and lacked long-term follow-up data. The number of patients included in this research was small, especially female patients. Although the results showed that the total retinal TTI of female patients was significantly higher than that of the control group, the TTI of IRLs did not show a significant difference compared with the control group, which was different from male patients. Therefore, more female cases are needed for further investigation. Moreover, we did not include AS patients who had other hereditary modes. The OCT measurement results were different with histologic status. Therefore, histological study is expected to determine the microstructure change of AS retina change. Although the frequency and severity of typical ocular anomalies increase with age[8], we did not find a correlation between the TTI and patient age, and we did not analyze whether retinal thinning correlates with renal function. Whether temporal retinal thinning worsens as the disease progresses is unknown, and further study is needed. It should be noted the axis length and refractive error may affect the retinal thickness. To reduce the impact caused by axis length, we excluded the participants with high myopia or hyperpresbyopia.

In conclusion, our study analyzed the temporal retinal thinning characteristics with the automated segmentation algorithm of SD-OCT. We identified that temporal retinal thinning appeared early in XLAS patients and was mainly caused by structural abnormalities of the inner retina. This noninvasive examination could be helpful for the early diagnosis and follow-up of AS.

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