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UTILITY OF ORAL FLUORESCEIN ANGIOGRAPHY WITH ULTRA-WIDEFIELD IMAGING SYSTEM FOR EVALUATION OF VARIOUS RETINAL DISORDERS

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Purpose: To evaluate the utility of oral fluorescein angiography with ultra-widefield imaging system (oral UWF-FA) predominantly in children.

Methods: We recruited 17 patients aged 2 years to 22 years with retinal disorders. Each patient ingested a dose of fluorescein sodium set by body weight mixed with 100 mL of juice. Images were scored using four parameters as follows: branch retinal vessel identification, retinal vessels visualization, foveal avascular zone visualization, and clinically important findings such as leakage, microaneurysms, neovascularization, or significant nonperfusion area visualization. Based on the aggregate score, we classified the image quality into three grades.

Results: Sixteen of 17 patients completely ingested the fluorescein sodium, and ultra-widefield fluorescein angiography was performed. Images were classified as high quality in nine cases, moderate quality in four, and poor quality in three. In 13 cases (81.3%), images had adequate quality to evaluate retinal conditions. Of three patients with poor-quality images, 2 took 10 minutes to ingest fluorescein sodium and the other ingested only half the dose. The adverse event of a mild skin rash was noted in one patient.

Conclusion: Oral ultra-widefield fluorescein angiography is effective in evaluating retinal pathology and is a useful alternative especially for pediatric patients who cannot tolerate intravenous line placement.

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The ultra-widefield (UWF) imaging system has been widely used as a retinal image evaluation device. The UWF imaging system can image 200° of the retina in a single image in 0.4 seconds. It is also capable of fluorescein angiography (FA) transiting the same 200° area, which is useful for evaluating not only for posterior retinal conditions but also for the peripheral retinal conditions. Recently, the optical coherence tomography angiography (OCTA) has been developed and is gaining popularity. One major reason for this popularity is that it does not require intravenous fluorescein sodium, which has potential adverse effects, such as nausea, vomiting, venipuncture, extravasation, and life-threatening anaphylactic shock. However, currently, OCTA has several limitations, including narrow-field imaging and inability to evaluate the leakage from neovascular vessels. Therefore, it is unrealistic that FA can be eliminated from our daily clinical practice, especially in the evaluation of neovascular ocular diseases, such as diabetic retinopathy, retinal vein occlusion, and age-related macular degeneration. In pediatric retina practice, FA is useful in evaluating disease activity of various diseases, such as retinopathy of prematurity, familial exudative vitreoretinopathy, and Coats disease. However,

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pediatric patients often do not cooperate with FA because it requires administration of intravenous dye. Fluorescein angiography with oral intake of fluorescein sodium (oral FA) has been proposed as an alternative to FA with intravenous injection of fluorescein sodium (IVFA).[1–4] Oral FA produces inferior quality images with a conventional fundus camera;[2–4] however, using a scanning laser ophthalmoscope solves the problem.[5–7] The UWF imaging system also uses the scanning laser ophthalmoscope with a higher sensitive camera. Recently, although UWF-FA with intravenous injection of fluorescein sodium (UWF-IVFA) has been widely reported,[8,9] there have been only a few reports on the use of oral UWF-FA.[10–12] We report our oral UWF-FA experiences predominantly in pediatric patients with various retinal disorders.

Materials and Methods

Patient Selection and Characteristics

This study was conducted from July 2014 to January 2019 at Kindai University Hospital and adhered to the tenets of the Declaration of Helsinki. This study was approved by the Institutional Review Board of the Kindai University Faculty of Medicine (#25-202). Oral FA involves off-label usage of fluorescein sodium. Hence, the first choice of FA during the study period was IVFA. We explained in detail about oral FA and IVFA to patients and their parents or guardians who were not likely to be cooperative for IVFA and or who refused IVFA mainly because of the placement of a painful peripheral venous infusion line, and the decision to choose was left to them. Written informed consent was obtained from all the adult patients and parents or guardians of minors. Seventeen patients ranging in age from 2 years and 11 months to 22 years were recruited in this study. There were 11 boys, five girls, and a 22-year-old man. Eleven of 17 patients (65%) were 6 years old or younger. Except for a 22-year-old man, all the other patients were 12 years old or younger. Clinical diagnoses included 10 cases of familial exudative vitreoretinopathy (FEVR), five cases of Coats disease, one case of uveitis, and one case of cytomegalovirus retinitis. Two cases of a 22-year-old man with FEVR and a 10-year-old boy with cytomegalovirus retinitis had an adverse event history of nausea on previous intravenous injection of fluorescein sodium. For evaluations of treatment for the diseases, three cases received oral UWF-FA twice, before, and after treatment.

Oral Fluorescein Sodium Intake and Angiography Protocols

The patients' pupils were pharmacologically dilated before imaging was performed. Ultra-widefield scanning laser ophthalmoscope (Optos California or 200Tx, Optos plc; Dunfermline, Scotland, United Kingdom) was used for noncontact high-resolution retinal angiograms. Approximately, 25 mg/kg of 10% fluorescein sodium (Fluorescite; Novartis Pharma, Basel, Switzerland) was mixed with 100 mL of fruit juice. The patients were instructed to ingest the fluorescein sodium as quickly as possible. Two patients who had nausea previously due to intravenous injection of fluorescein sodium were given 15 mg/kg of 10% fluorescein sodium with 100 mL of juice. When patients completed the full dose of fluorescein sodium, the imaging system timer was started. The images were obtained every minute until the late arteriovenous phase was reached, and then, every 5 minutes until the late phase was reached.

Image Analysis

For quantitative evaluation of the utility of oral UWF-FA, the image quality scoring was performed by five experienced retina specialists. They were blinded to the patients' clinical information and performed the scoring independently. To score the images, we used four different image quality parameters, which were modified from the methods previously used by Amador-Patarroyo, Squirrell, and Garcia et al.[5–7] The four parameters were: (I) the branch retinal vessel identification, (II) the retinal vessels visualization, (III) the foveal avascular zone (FAZ) visualization, and (IV) the clinically important findings, such as the absence or presence of leakage, microaneurysms, neovascularization, or significant nonperfusion area visualization. In the scoring of parameters (II), (III), and (IV), each observer used the UWF-IVFA images obtained in usual clinical practice as comparisons for the oral UWF-FA images. All the parameters were scored using a three-point scale as follows, (I): 0 points; first-order branch not seen, one point; only first-order branch seen, two points; second-order branch or more seen, (II): 0 points; poor, one point; intermediate, two points; equivalent to images by UWF-IVFA, (III): 0 points; impossible to judge, one point; seen but not clearly, two points; seen equivalent to images by UWF-IVFA, and (IV): 0 points; impossible to judge, one point; seen but not clearly, two points; seen equivalent to images by UWF-IVFA. Depending on the fundus findings, FAZ may not be determined regardless of methods of fluorescein sodium administration. Therefore, in the scoring of parameter (III), we

selected a better score for each of the right and left eyes. For all parameters, we calculated interobserver agreement using the kappa statistic. Kappa values were interpreted as follows: <0.00, poor agreement; 0.00 to 0.20, slight agreement; 0.21 to 0.40, fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.80, substantial agreement; and 0.81 to 1.00, almost perfect agreement. We evaluated the sum of each score as an indicator of image quality. To evaluate the image quality based on the score of each parameter, all observers were asked about the score of each parameter needed for the images to be clinically useful. All of them answered that parameter (I) required two points, and parameters (II), (III), and (IV) required one point for them to judge the clinical retinal conditions from the images. Based on their answers and the total score of each image, we classified the images into the following three grades. The image with a maximum of eight points was defined as high quality, which had almost equivalent quality as that of images by UWF-IVFA. The total score required for the clinically useful quality determined by all observers was five points or more. Therefore, total scores of five, six, and seven points were defined as moderate quality, and four points or less as poor quality. Even if one parameter score had zero points, the image was classified as poor quality.

Statistical Analysis

Interobserver agreement was assessed using the kappa statistics. For multiple observers, we calculated the kappa values for pairs of observers and then computed an average kappa value for all possible pairs.[13] Statistical analysis was performed using JMP version 13.0 software (SAS Institute Inc, Cary, NC).

Results

Patients Characteristics

The characteristics of the 17 cases are shown in Table 1. Sixteen of 17 cases were able to ingest the fluorescein sodium. A 10-year-old boy with cytomegalovirus retinitis (Case 17) denied because of the bitter flavor of fluorescein sodium. In the other 16 cases, oral UWF-FA was performed. In Cases 14 and 15, however, it took more than 10 minutes for ingestion of the full-fluorescein sodium despite being instructed to ingest it as quickly as possible. Case 14, the youngest girl, 2 years and 11 months, cooperated for UWF-FA. We did not hold her during the examination because could put her chin on the chin rest according to our instruction.

Image Quality Analysis

Of the four parameters used for scoring, for parameter (I), all observers gave two points in all cases. The scores for the other three parameters varied within one point between observers. Figure 1 shows representative images of each score of parameters (II), (III), and (IV). Of the 16 cases who completed oral UWF-FA, 9 cases were classified as high quality, 4 were moderate quality, and 3

Table 1. Summary of 17 Cases

Case No.	Age, years	Sex	Disease	Oral Intake Time of Fluorescein Sodium	Adverse Event	Images' Total Score	Image Quality	Time to the First Image, minutes
1	4	M	FEVR	In one gulp	None	8	High	5
2	4	F	FEVR	In one gulp	None	8	High	4
3	5	M	FEVR	In one gulp	None	8	High	6
4	6	M	Coats disease	In one gulp	None	8	High	4
5	6	M	Coats disease	In one gulp	None	8	High	4
6	6	F	FEVR	In one gulp	None	8	High	8
7	7	M	Uveitis	In one gulp	None	8	High	8
8	9	M	Coats disease	In one gulp	None	8	High	7
9	10	M	Coats disease	In one gulp	None	8	High	4
10	4	F	FEVR	In one gulp	None	6∼7	Moderate	4
11	5	M	FEVR	In one gulp	None	6∼7	Moderate	7
12	6	M	Coats disease	In one gulp	None	6∼7	Moderate	4
13	12	M	Coats disease	In one gulp	None	5∼7	Moderate	6
14	2	F	FEVR	10 minutes	None	2∼3	Poor	28
15	4	F	FEVR	10 minutes	None	2∼4	Poor	30
16	22	M	FEVR	Half dose In one gulp	Mild skin rash	2∼4	Poor	4
17	10	M	Cytomegalovirus retinitis	Could not ingest	—	—	—	—

F, female; M, male.

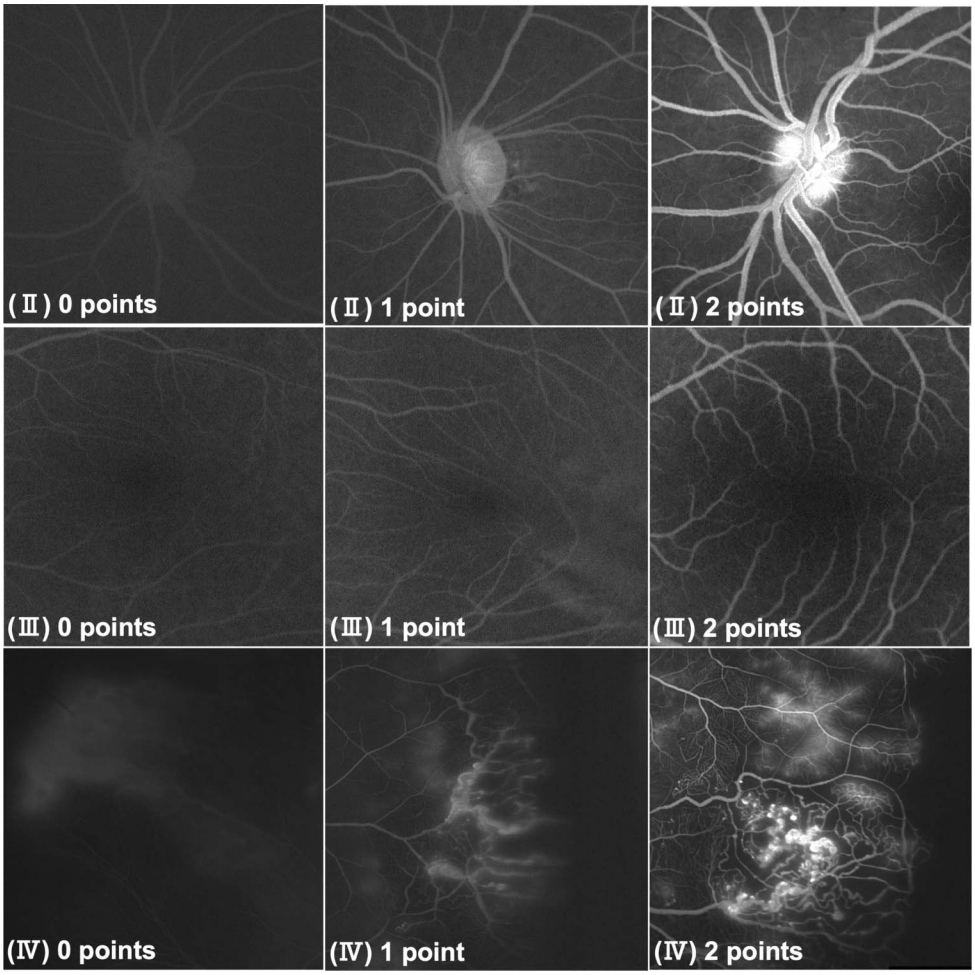

Fig. 1. Representative images of each score of parameters (**II**), (**III**), and (**IV**). The representative images of each score of parameters (**II**), (**III**), and (**IV**) are shown. Each image was selected from images for which all observers gave the same score. Upper row: Parameter (II) Visualization of the retinal vessels: 0 points; poor, one point; intermediate, two points; equivalent to images by UWF-IVFA. Middle row: Parameter (III) The FAZ visualization: 0 points; impossible to judge, one point; seen but not clearly, two points; equivalent to images by UWF-IVFA. Lower row: Parameter (IV) Clinically important findings, such as the absence or presence of leakage, microaneurysms, neovascularization, or significant nonperfusion area, visualization: 0 points; impossible to judge, one point; seen but not clearly, two points; equivalent to images by UWF-IVFA.

were poor quality (Table 1). In 9 of 16 cases (56.3%), obtained images were judged to be equivalent to images of UWF-IVFA. In 13 of 16 cases (81.3%), obtained images were judged to be clinically useful. Figure 2 shows representative images of Case 2 with FEVR classified as high quality, to which all observers gave perfect scores. The peripheral nonperfusion area with leaking telangiectatic vessels in the temporal peripheral retina is clearly visible. Three cases (Cases 14, 15, and 16) were classified as poor quality. Two of the 3 cases (Cases 14 and 15) took more than 10 minutes for ingestion of the fluorescein sodium. Figure 3 shows images of Case 15 with FEVR classified as poor quality. Images obtained at 50 minutes after oral intake showed low contrast because of which it was difficult to evaluate the disease activity accurately. Furthermore, Case 16 classified as poor quality was administered half a dose of fluorescein sodium as compared with the others because of a history of nausea at the previous IVFA. Figure 4 compares images obtained by UWF-IVFA and oral UWF-FA. The total score using our scoring system for UWF-IVFA and oral UWF-FA were 5∼7 and 2∼4 points, respectively. Apparently, in this particular case with half-dose oral fluorescein sodium, the quality of oral UWF-FA images was inferior to that of UWF-IVFA.

Reproducibility of the Image Quality

We performed oral UWF-FA twice, before, and after surgery, in three cases (Cases 2, 3, and 4). In two of the three cases, images were classified as high quality both in the first and the second time. Figure 2 shows the images before and after the operation in Case 2. Both images were classified as high quality and sufficiently useful for evaluating the disease activity. On the other hand, in Case 4, all observers gave the first images a maximum of eight points, whereas they gave the second images a total score of five points. Figure 5 shows the images obtained in the first and second oral UWF-FA in Case 4. In the first examination, he could ingest the fluorescein

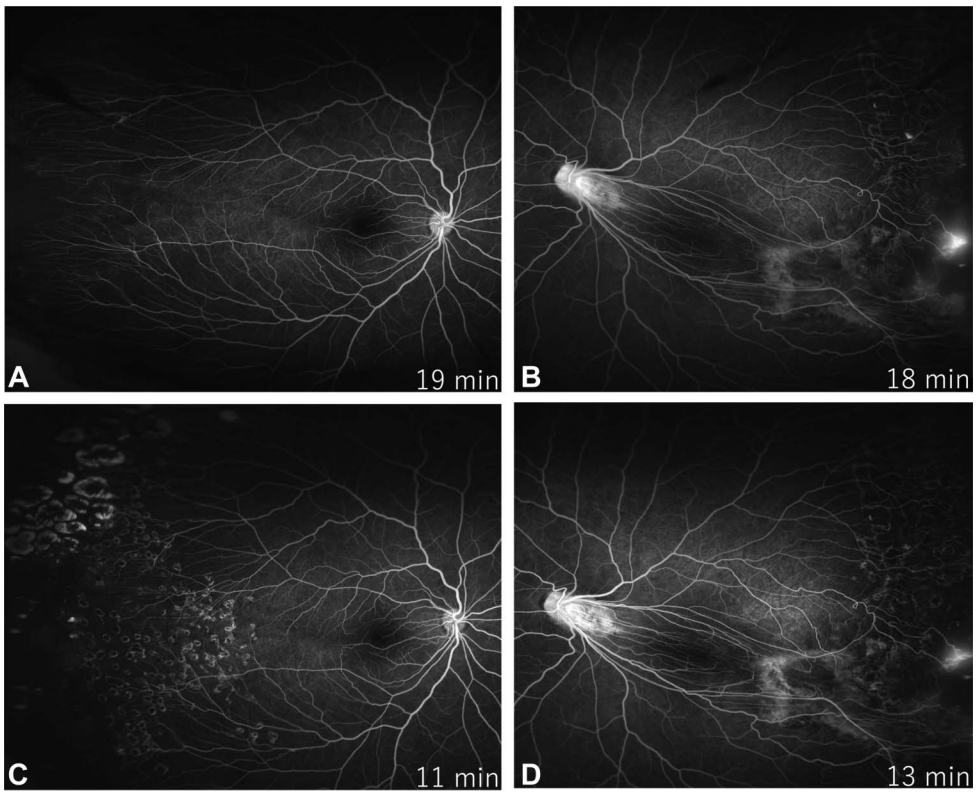

Fig. 2. Images of Case 2 (a 4-year-old girl with familial exudative vitreoretinopathy). **A.** Right eye before treatment. **B.** Left eye before treatment. **C.** Right eye after treatment. **D.** Left eye after treatment. All images were classified as high quality by all observers. **A.** and **B.** (before treatment): Bulbous vascular endings or telangiectasias and supernumerary vascular branching observed at the terminal ends of vessels abutting the vascular–avascular junction. Peripheral laser scars are visible. **C.** and **D.** (after treatment): Additional laser scars are visible at the peripheral nonperfusion area in the images before treatment.

sodium in one gulp, whereas it took 5 minutes in the second one.

Interobserver Agreement

The kappa values of each parameter were 1.00 for parameter (I), 0.90 for parameter (II), 0.59 for parameter (III), and 0.59 for parameter (IV). Overall, interobserver agreement was moderate to almost perfect for all parameters. Among all observers, the grading state by the total score was consistent in all cases.

Phase Wise Vascular Visualization After Oral Intake

We recorded the time interval between oral intake and the first image which showed the presence of fluorescein sodium in the major retinal vessels (Table 1). In all cases, except in Cases 14 and 15 where the images were classified as poor quality, the first images were obtained as early as 4 minutes and as late as 8 minutes after oral intake. The choroidal flush was not appreciated. After the first images, the late arteriovenous phase was visible, and the recirculation phase was visible no later than 17 minutes after oral intake. On the other hand, in Cases 14 and 15 where it took more than 10 minutes for ingestion of the fluorescein sodium, it took 30 minutes for fluorescein to be first visible, and subsequent gradual observation of the image was difficult because of poor image quality.

Adverse Events

An adverse event of mild skin rash, which resolved spontaneously after about an hour, in Case 16 who had a history of nausea was caused by the previous IVFA. In other cases, there were no adverse events after oral UWF-FA.

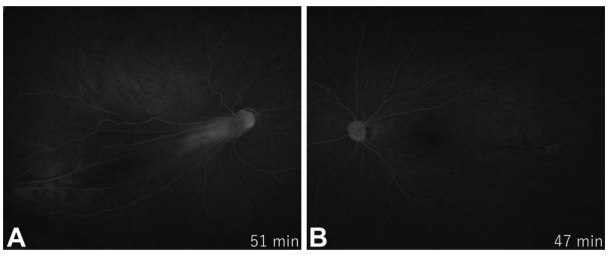

Fig. 3. Images of Case 15 (a 4-year-old girl with familial exudative vitreoretinopathy). **A.** Right eye. **B.** Left eye. Both images were classified as poor quality. The grading scores were as follows: (**I**) Branch identification; two points, (**II**) vessel visualization; 0 or one point, (**III**) FAZ visualization; 0 points, (**IV**) visualization of clinically important findings; 0 or one point, and total score was two, three or four points. She took 30 minutes to ingest the full fluorescein sodium.

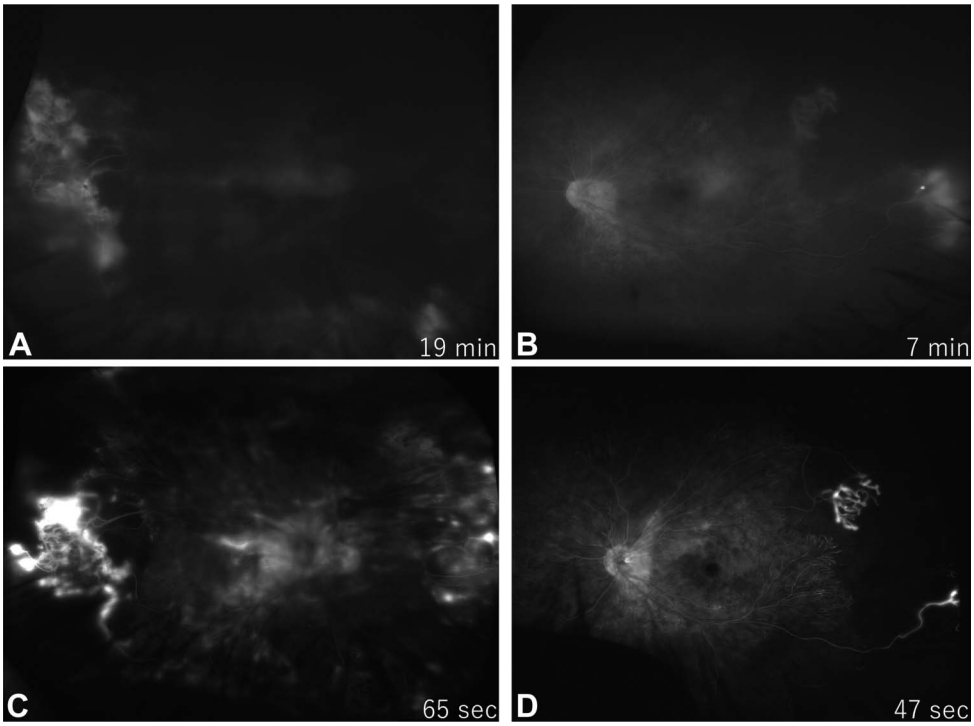

Fig. 4. Images of Case 16 (a 22-year-old man with familial exudative vitreoretinopathy). **A.** Right eye in oral UWF-FA. **B.** Left eye in oral UWF-FA. **C.** Right eye in UWF-IVFA. **D.** Left eye in UWF-IVFA. Both images by oral UWF-FA (**A** and **B**) were classified as poor quality. The grading scores were as follows: (**I**) branch identification; two points, (**II**) vessel visualization; 0 points, (**III**) FAZ visualization; 0 or one point, (**IV**) visualization of clinically important findings; one point, and the total score was three or four points. The image quality obtained by oral UWF-FA was inferior to that obtained by UWF-IVFA (**C** and **D**). The patient was administered half the dose of oral fluorescein sodium as compared with the others because of a history of nausea during a previous UWF-IVFA.

Discussion

In this study, we showed that oral UWF-FA was clinically useful for diagnosis and management of pediatric retinal disorders. In more than 80% of our cases, images with quality sufficient to evaluate the disease condition were obtained. To the best of our knowledge, this study is the first one to quantitatively evaluate the utility of oral UWF-FA in pediatric disorders. Especially for pediatric patients, oral intake of fluorescein sodium is more advantageous than conventional intravenous administration, as the former does not require placing a painful peripheral venous infusion line. This can reduce not only the patients' risk and discomfort but also labor and burden of the medical staff. To obtain clinically useful image quality with oral FA, we consider a couple of points to be important. First, the UWF imaging system should be used. It is equipped with a highly sensitive detector specialized for emission light of a fluorescein dye. Therefore, with UWF-FA, we can obtain higher quality images than images with a conventional fundus camera equipped with a conventional detector for light with a wide range of wavelengths. Second, the patients should ingest the appropriate dose of fluorescein sodium in a short time, ideally in one gulp. In our cases who did that, images had sufficient quality for diagnosis and management of typical pediatric retinal diseases, such as FEVR, Coats disease, and uveitis. Regarding the dose of fluorescein sodium, 25 mg/kg of body weight according to previous reports was administered orally.[2,3,10–12] In consideration of the bitter taste of fluorescein sodium, we mixed it with 100 mL of fruit juice. Although the concentration of fluorescein sodium in our study was lower than that of previous reports in which it was mixed with 30 mL of juice,[5,10,11] we could obtain clinically useful information in most cases. The time to obtain the first images was approximately the same as previously reported.[5,10,11] On the other hand, as shown as Figure 4, in Case 16 in which the dose of fluorescein sodium was half, all the images were considered as poor

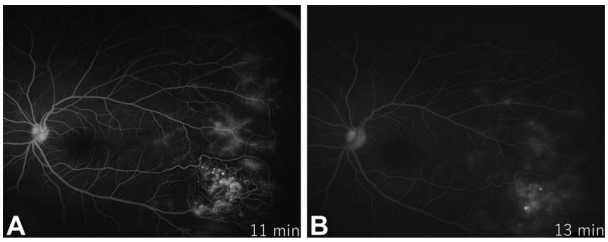

Fig. 5. Images of Case 4 (a 6-year-old boy with Coats disease). **A.** Left eye in the first oral UWF-FA. The image clearly shows leaking microaneurysms in the temporal area with nonperfusion areas. It was classified as high quality by all observers. The patient ingested the fluorescein sodium in one gulp in the first oral UWF-FA. **B.** Left eye in the second oral UWF-FA. The image was classified as moderate quality. The grading scores were as follows: (**I**) branch identification; two points, (**II**) vessel visualization; one point, (**III**) FAZ visualization; one or two points, (**IV**) visualization of clinically important findings; one or two points, and total score was five points. Compared with the first image, the second image shows a lower contrast. The patient took 5 minutes to ingest the full fluorescein sodium in the second time.

quality. Figure 5 shows images of Case 4, in which oral UWF-FA was taken twice, before, and after laser treatment. The image quality obtained in the first and second examinations was clearly different. In the second examination, where the image quality was poor, the patient took longer for ingestion of the fluorescein sodium. Similarly, in Cases 14 and 15, oral intake of fluorescein sodium took about 10 minutes, and the images were classified as poor quality. From these results, we consider that it is important to ingest the appropriate dose of fluorescein sodium in one gulp to ensure the required image quality with oral UWF-FA. In FA, vascular phase wise demarcation of choroidal and retinal circulation is one of the important factors for diagnosis or management of diseases. In our oral UWF-FA examination, the first images were the arterial phase or the arteriovenous phase. The choroidal flush was not appreciated in all cases. It was difficult to distinguish the classical FA phases as clearly as IVFA, probably because of the slow increase of the fluorescein sodium concentration compared with IVFA. However, the visualization of gradual changes of clinically important findings such as leakage, microaneurysms, and nonperfusion areas was quite possible as shown as Figure 6. It is generally assumed that the adverse reaction rate and severity is lesser with oral intake than with intravenous injection.[1,2,4,7] No severe adverse events have been previously reported after oral FA. In our study, an adverse event occurred only in Case 17. The patient had only a mild skin rash, whereas nausea was seen with the previous IVFA. No other adverse events were seen in other cases. However, because of the small number of cases in this study, it is impossible to evaluate the safety of oral FA from our results. Oral UWF-FA has some disadvantages. First, it involves off-label usage of fluorescein sodium and requires institutional review board approval. It is necessary to consider the cost-benefit ratio according to the medical insurance system in each country. Second, if the patients cannot tolerate oral intake of the fluorescein sodium, the examination cannot be performed. Third, it is difficult to obtain information on indicators of ocular circulation, such as choroidal flush and arm-to-retina circulation time, and to distinguish the classical FA phases as clearly as IVFA. Therefore, oral UWF-FA is not likely to replace IVFA. However, considering the advantages mentioned above, we believe that it is a useful, convenient mode of examination, and an alternative to IVFA, especially for pediatric patients who are uncooperative with intravenous line placement and have difficulty concentrating for a long time during the examination. In conclusion, our study showed that most images obtained by oral UWF-FA were clinically useful. Although this method will not replace IVFA, it is a useful alternative with equivalent image quality to IVFA, especially for pediatric patients.

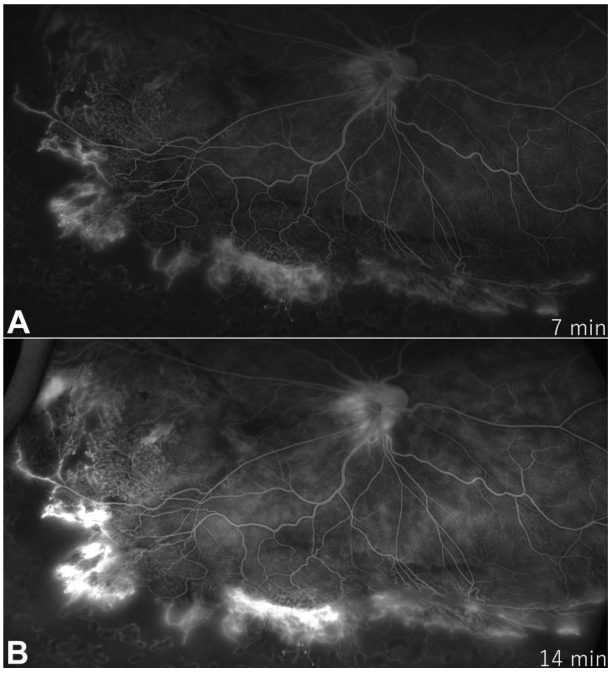

Fig. 6. Images of Case 3 (a 5-year-old boy with familial exudative vitreoretinopathy). **A.** Right eye 7 minutes after oral intake. **B.** Right eye 14 minutes after oral intake. Both images were classified as high quality by all observers. Prominent temporal vascular dragging, hyperfluorescence, and leakage from neovascularization are clearly visible. It can be appreciated that the leakage from neovascularization increases with time.

Key words: Coats disease, familial exudative vitreoretinopathy, fluorescein angiography, intake of fluorescein sodium, oral fluorescein angiography, pediatric patient, pediatric retinal disorder, ultra-wide-field imaging system, uveitis.

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