

Case Report

Retinal Capillary Abnormalities in Sjögren-Larsson Syndrome Maculopathy

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Keywords

Foveal avascular zone · Maculopathy · Optical coherence tomography angiography · Retinal capillaries · Sjögren-Larsson syndrome

Abstract

Sjögren-Larsson syndrome (SLS) is a neurometabolic disease with a peculiar crystalline maculopathy. It is yet unclear if vascular abnormalities play a role in SLS maculopathy pathogenesis. We used optical coherence tomography angiography (OCT-A) to search for vessel abnormalities in SLS maculopathy. We performed a cross-sectional study in 4 patients (2 males, 2 females, aged 12–36 years) with various stages of SLS maculopathy. Besides OCT-A imaging, a complete ophthalmological examination and additional retinal imaging by transversal and *en face* spectral domain (SD) OCT were performed. OCT-A images were qualitatively assessed for vascular abnormalities, and imaging was compared to eight eyes of four healthy controls. On OCT-A, all eyes of patients with SLS showed a reduced capillary density around the fovea, and an enlarged foveal avascular zone (FAZ; SLS patients [$n = 6$ eyes] mean 0.70 mm² [SD 0.18]; healthy controls [$n = 8$ eyes] mean 0.34 mm² [SD 0.07], $p = 0.004$). In 2 patients, telangiectatic vessels were seen in the deep capillary layer. In conclusion, OCT angiography showed capillary paucity and morphological vessel abnormalities in these 4 patients with SLS.

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Introduction

Sjögren-Larsson syndrome (SLS) is an autosomal recessive inherited metabolic disorder, caused by the deficiency of fatty aldehyde dehydrogenase, due to a genetic defect in the *ALDH3A2* gene. The syndrome is clinically characterized by intellectual disability, bilateral spasticity, and ichthyosis. Next to this classical clinical triad, all patients suffer from reduced visual acuity and photophobia due to a pathognomonic crystalline macular dystrophy. This maculopathy is characterized by a thinning of the fovea, crystalloid deposits in the parafovea, foveal pseudocysts [1], and a lack of macular pigment [2].

In a recent study, we observed that disease progression can be divided into 4 stages of SLS maculopathy according to spectral domain optical coherence tomography (SD-OCT) findings [3]. Stage 1 maculopathy is characterized by a thin and immature structured fovea with lack of macular pigment, apparently reflecting an arrested foveal development around birth, and presence of intraretinal crystals. On top of the developmental disorder, macular degeneration may occur by phototoxic damage, first marked by the appearance of foveal pseudocysts (stage 2), and followed by disappearance of these pseudocysts and occurrence of photoreceptor damage with lipofuscin accumulation (stage 3). Eventually, SLS maculopathy may progress to end-stage macular degeneration with frank atrophy of the retinal pigment epithelium or neovascularization (stage 4).

It is yet unclear if vascular abnormalities are also present in SLS maculopathy. In an early study [4], our group was able to examine retinal perfusion by fluorescein angiography in 3 patients with SLS. All patients showed a mottled hyperfluorescence of the macula without leakage in late stage, but no structural vessel abnormalities were observed at that time.

Optical coherence tomography angiography (OCT-A) is a novel, noninvasive imaging technique that enables high-resolution visualization of ocular blood flow in three dimensions without the injection of dyes. The technique appeared useful in several vascular retinal diseases like wet age-related macular degeneration or diabetic retinopathy [5, 6]. In our current study, we applied OCT-A to search for vessel abnormalities in SLS maculopathy.

Case Presentation

We performed a cross-sectional cohort study in patients with SLS. The study was performed according to the tenets of the declaration of Helsinki (2013 revision) and was approved by the Regional Committee on Research Involving Human Subjects. Informed consent was obtained from all participants and their parents or legal representatives prior to inclusion in the study. All patients were seen in our outpatient clinic between April and November 2017.

All known Dutch patients with SLS ($n = 35$) were invited to participate in the study. The diagnosis of SLS was already genetically confirmed in all patients. Patients had to be able to sit still for a few minutes in order to achieve acceptable OCT-A scans.

Besides OCT-A examination, all patients underwent complete ophthalmologic examination, including best-corrected visual acuity, slit lamp biomicroscopy and ophthalmoscopy. Before ophthalmologic examination and imaging of the retina, pupils were dilated by one drop of tropicamide 0.5% and one drop of phenylephrine 2.5%. In addition, patients underwent color fundus photography next to transversal and *en face* SD-OCT. The SD-OCT scans were previously used in an extended study published in 2019 [3].

The Spectralis™ 2 device (Heidelberg Engineering, Heidelberg, Germany) was applied for retinal SD-OCT and OCT-A imaging. All scans were performed by one of the authors (PS). The regular OCT-A scanning protocol (512 B-scans and pattern size of 3.0×3.0 mm) was adjusted

Table 1. Study results of patients with SLS

Patient				Visual acuity	OCT-A scanning protocol			SD-OCT results	OCT-A results
no.	sex (M/F)	age, years	eye	BCVA (Snellen)	B-scans, <i>n</i>	pattern size, mm	distance between B-scans, μm	SLS maculopathy stage*	FAZ surface area, mm^2
1	F	12	OD	20/40	256	3.0×1.5	6	1	0.73
			OS	20/40	256	3.0×1.5	6	1	0.97
2	M	13	OD	20/100	256	3.0×1.5	6	2	0.64
			OS	20/100	256	3.0×1.5	6	2	NR
3	M	25	OD	20/63	512	3.3×3.3	6	2	0.50
			OS	20/50	512	3.4×3.4	7	2	0.52
4	F	36	OD	20/63	423	3.0×2.5	6	4	0.85
			OS	20/63	214	3.0×1.2	6	4	NR

BCVA, best-corrected visual acuity; F, female; FAZ, foveal avascular zone; M, male; NR, not recordable; OCT-A, optical coherence tomography angiography; OD, right eye; OS, left eye; SD-OCT, spectral domain optical coherence tomography.

*SLS maculopathy stages according to Staps et al. [3].

to a faster scanning protocol (less B-scans and smaller pattern size; see Table 1 for details) in 3 of the 4 patients due to poor cooperation of the disabled patients, to acquire sufficient quality scans. Imaging resulted in two high-density retinal cubes per eye, i.e., an SD-OCT volume scan to analyze structural retinal aspects and a corresponding flow cube to study the structure of retinal blood flow.

Image analysis and image optimization before analysis were all performed by the Heidelberg Eye Explorer™, version 6.9.5.0 (Heidelberg Engineering, Heidelberg, Germany). Automatic projection artifact removal included in the software was applied to all OCT-A images to avoid misinterpretation of vessel flow aspects and vessel density in the outer retina by signals arising from inner retinal layers. The optimal contrast for each layer was manually chosen. We quantitatively examined the vascular layers provided in the Heidelberg Eye Explorer™, namely the total retina (measured from the inner limiting membrane to the outer photoreceptor layer [PR2]), superficial vascular complex, and deep vascular complex. We did not choose for a more delicate vascular layer segmentation because due to the limited retinal thickness of the patients with SLS, segmentation of the intermediate capillary layer could not have been performed reliable and reproducible. In each vascular layer, we qualitatively assessed the capillary pattern, intercapillary spaces, and the foveal avascular zone (FAZ) outline and shape. In addition, the FAZ area was measured manually using the measurement tool of the Heidelberg Eye Explorer™, in the total retina vessel volumes of SLS cases. All SLS imaging data were compared to scans of healthy controls who were available in our database and had complete and normal scans without abnormalities. We have randomly assigned healthy controls from our database by coin flipping.

FAZ areas are presented as means with standard deviations (SD). The Student's *t* test was used to test for differences in FAZ area in patients with SLS compared to healthy controls. A *p* value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 25 for Windows (SPSS, Chicago, IL, USA).

Seventeen of the 35 invited patients with a classical SLS phenotype agreed to participate in our current study (extension of the study published in 2019 by Staps et al. [3]). In eight of these patients, OCT-A scans could be captured. The remaining 9 patients were not able to the retinal angiogenesis [10], and without Müller cells, neuronal and vessel degeneration may

cooperate sufficiently to perform OCT-A scans at all. Of the 8 patients with OCT-A scans performed, 7 eyes of 4 patients were of sufficient quality for further analysis and were included in the study (2 males, 2 females, aged 12–36 years; Table 1). Study scans were compared to 8 scans of four healthy controls that were available in our database (4 females, aged 24–28 years). The patients and controls were scanned on the same OCT-A device.

All study patients had a reduced best-corrected visual acuity within the range 20/100–20/40 (Snellen). Ophthalmologic examination showed no abnormalities in the anterior segment. A poorly pigmented macula with the characteristic crystals was seen by ophthalmoscopy in all cases. We observed different stages of SLS maculopathy on SD-OCT scanning (Table 1). Patient 1 showed a grade 1 maculopathy with hyperreflective dots (see arrows) and a thin macula. Patients 2 and 3 showed a foveal pseudocyst (arrows) and interruption of the photoreceptor layer, corresponding with grade 2 SLS maculopathy. In patient 4, retinal pigment epithelium involvement (see arrows, the white stapling of lipofuscin is seen in patient 4) was seen on SD-OCT imaging, corresponding with a grade 4 SLS maculopathy (Fig. 1).

The quality of the OCT-A scans of the patients with SLS was sufficient for qualitative analysis, but too poor for quantitative measurements, such as vessel density, tortuosity, or fractional dimension. However, manual measurement of the FAZ surface area was possible in 6 of 7 study eyes.

In Figure 2, all OCT-A scans including *en face* images of all right eyes of the 4 SLS patients and one eye of a healthy control are shown. On the *en face* SD-OCT scans, one or more pseudocysts (dark areas, see asterisk in patient 4) of various sizes were observed, colocalizing with the superficial vascular complex in all cases. Furthermore, the patients showed multiple hyperreflective dots (light spots, see arrow in patient 2) around the fovea in both vessel layers. In cases 1–3, one or more pseudocysts were also visible colocalized with the deep retinal vessel layers. None of the SLS cases showed the foveal hyperreflectance visible in the foveal umbo of normal controls (see arrow). OCT-A images of the SLS cases showed a decreased capillary flow density in the perifoveal area, mainly in the deep vascular complex. Furthermore, the capillaries showed an irregular pattern in all SLS patients, compared to the more integrated pattern in the healthy controls. No right-angled capillaries were seen. In patients 1 (left eye) and 3 (right eye), focal thickening of vascular flow signals at the border of the FAZ suggested the presence of telangiectatic vessels in the deep retinal vessel layers (Fig. 3). The FAZ surface area was measured larger in patients with SLS compared to the healthy controls (SLS patients [$n = 6$ eyes] mean 0.70 mm^2 [SD 0.18]; healthy controls [$n = 8$ eyes] mean 0.34 mm^2 [SD 0.07]), and this was statistically significant ($p = 0.004$, Student's t test).

Discussion

In this cross-sectional cohort study, we examined patients with SLS by OCT-A to investigate retinal vessel appearance in the various stages of SLS maculopathy. All patients with SLS showed an abnormal vascular anatomy, with a reduced capillary density around the fovea, an irregular pattern of capillaries, and a larger FAZ surface area. Furthermore, 2 patients showed telangiectasia.

SLS maculopathy was previously compared to cases with macular telangiectasia (MacTel) type 2a [7]. Both diseases are characterized by the loss of macular pigment presumably by Müller cell deficiency. As observed in SLS maculopathy in our present study, MacTel also appeared to have reduced perifoveal capillary density [8]. The reduced capillary density seen in our cohort was also observed in a small group of older SLS patients [9]. It has been shown that Müller cells and retinal capillaries have a close cooperation. Müller cells are involved in

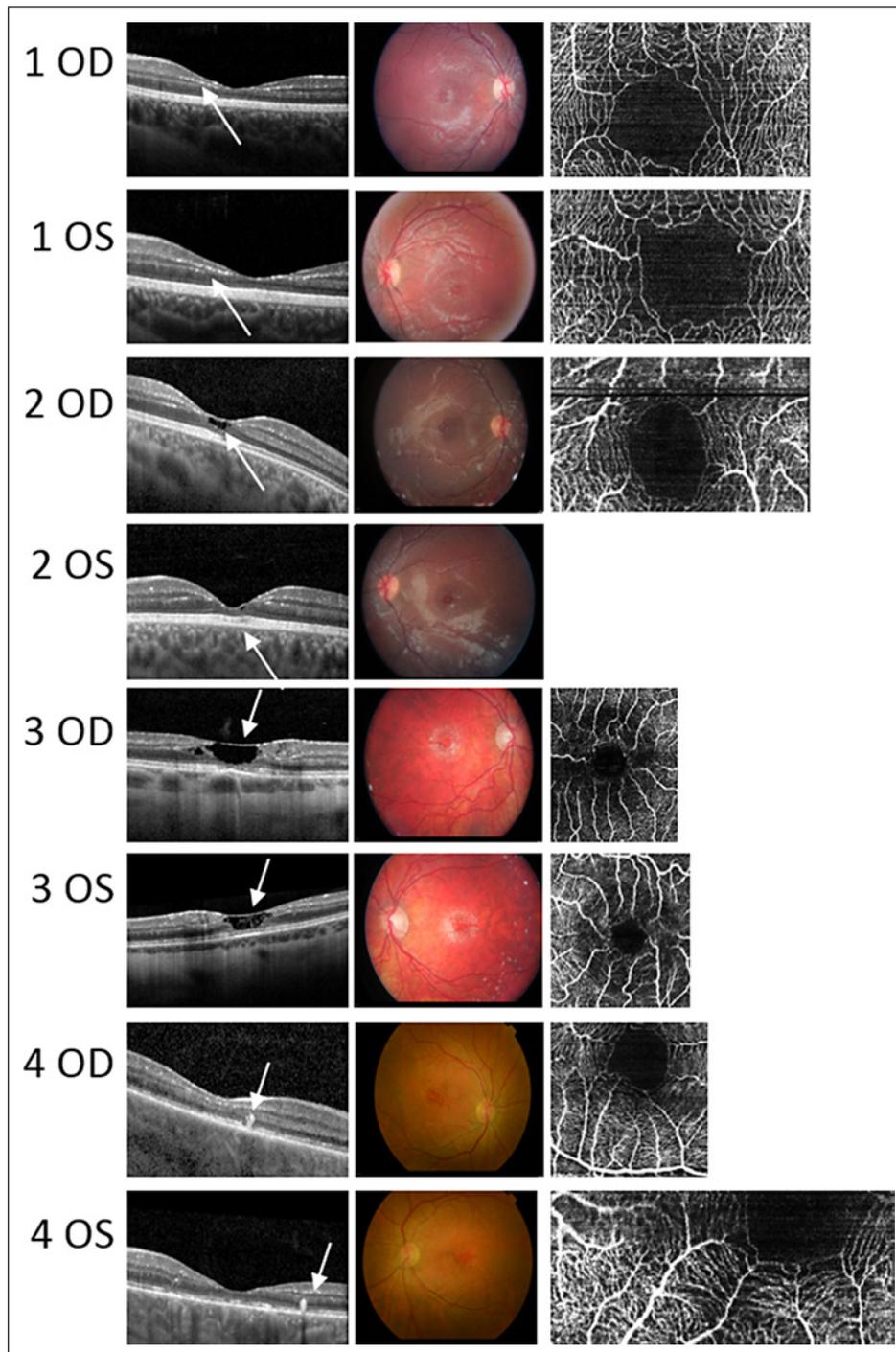


Fig. 1. SD-OCT images* of the four SLS patients (patient numbers 1–4, “OD” for right eyes, “OS” for left eyes) are shown in the left semicolumn **(a)**. Corresponding fundus photography is shown in the middle semicolumn **(b)**, and OCT angiography (OCT-A) images of the total retina are shown at the right semicolumn **(c)**. Patient 1 shows a grade 1 SLS maculopathy with hyperreflective dots (arrow) and a thin macula. Patients 2 and 3 show small (patient 2) and large (patient 3) foveal pseudocysts (pointed to with arrows) and consecutive interruption of the photoreceptor layer, corresponding with grade 2 SLS maculopathy. In patient 4, RPE involvement is seen on SD-OCT (arrows), corresponding with a grade 4 SLS maculopathy. In all patients, the characteristic perifoveal crystals are seen in the fundus photography (b column). * SD-OCT images 1 OD, 3 OD, and 4 OD have been previously shown in the paper by Staps et al. [3]. RPE, retinal pigment epithelium.

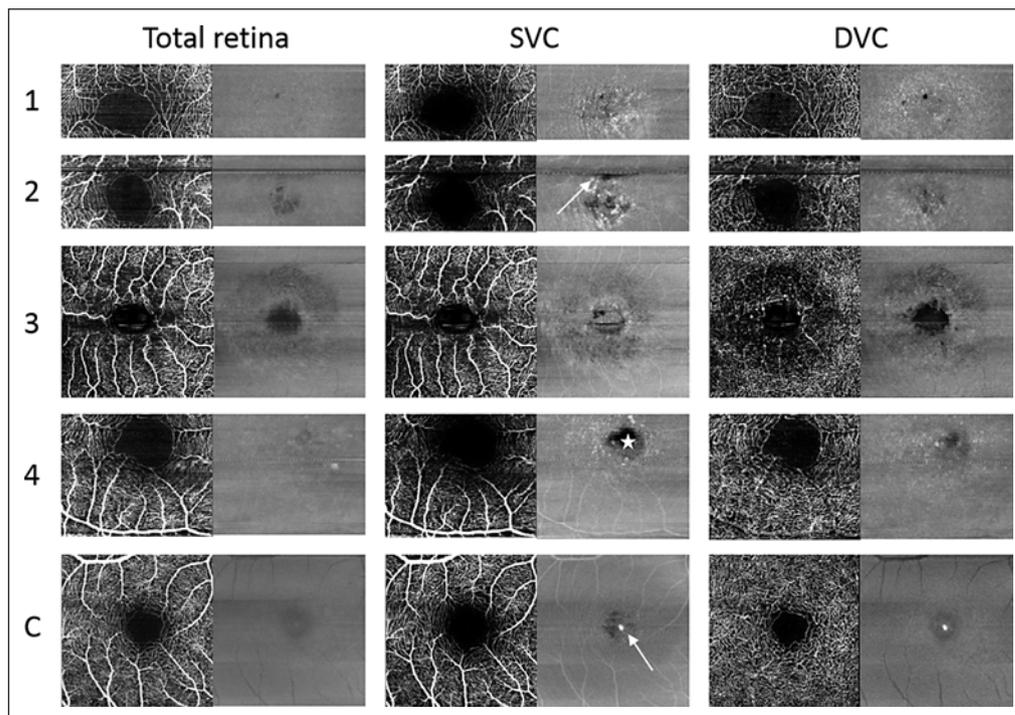


Fig. 2. OCT-A (left columns) and *en face* reflectance OCT (right columns) images of four right eyes of four SLS patients (1–4) and a normal control (C). The SVC shows one or more retinal pseudocysts (dark areas, asterisk in patient 4) of various sizes together with multiple hyperreflective dots (light spots, arrow in patient 2) around the fovea on *en face* reflectance images. In cases 1–3, one or more pseudocysts are also visible in the DVC. None of the SLS cases showed the foveal hyperreflectance visible in the umbo of the normal controls (white dot in the middle and right columns, last row, see arrow). OCT-A images of SLS cases show a larger FAZ than the control. The perifoveal capillary flow appears to be decreased in the DVC in all cases. In cases 2 and 3, focal thickening of the flow signal in the DVC suggests the presence of telangiectatic retinal vessels. DVC, deep retinal vessel complex; SVC, superficial vascular complex; OCT, optical coherence tomography.

occur [11]. In addition, if Müller cell damage occurs, neovascularization may be stimulated by paracrine mechanisms [10]. Retinal telangiectasia may be an early sign of this process [12]. All those processes can be observed both in SLS and in MacTel. Therefore, similar pathological mechanisms may be suspected, which lead to the final stages of maculopathy.

SLS with congenital loss of Müller cells may serve as a model for early macular degeneration, which is supported by our recent SD-OCT findings [3]. The reduced perifoveal capillary density in OCT-A scans of the patients with SLS could be supportive to our hypothesis of a retinal developmental arrest in SLS. In SLS related macular degeneration, affected Müller cells may trigger an arrest in angiogenesis and may cause the irregular pattern and rarefaction of retinal capillaries and the appearance of telangiectasia. Telangiectasia was also observed in a study in rodents that were genetically modified to have Müller cell ablation during development [13]. Our hypothesis of an arrest in retinal development causing the capillary abnormalities in SLS needs further investigation because the limited number of study patients does not allow to prove this hypothesis. The reduced perifoveal capillary density could also be a degeneration process as a result of the metabolic disease and accumulation of toxic fatty aldehydes and alcohols following initial normal retinal vessel development. Also, FAZ enlargement due to retinal pseudocysts causing a nondetection of vascular flow by segmentation faults must not be overlooked.

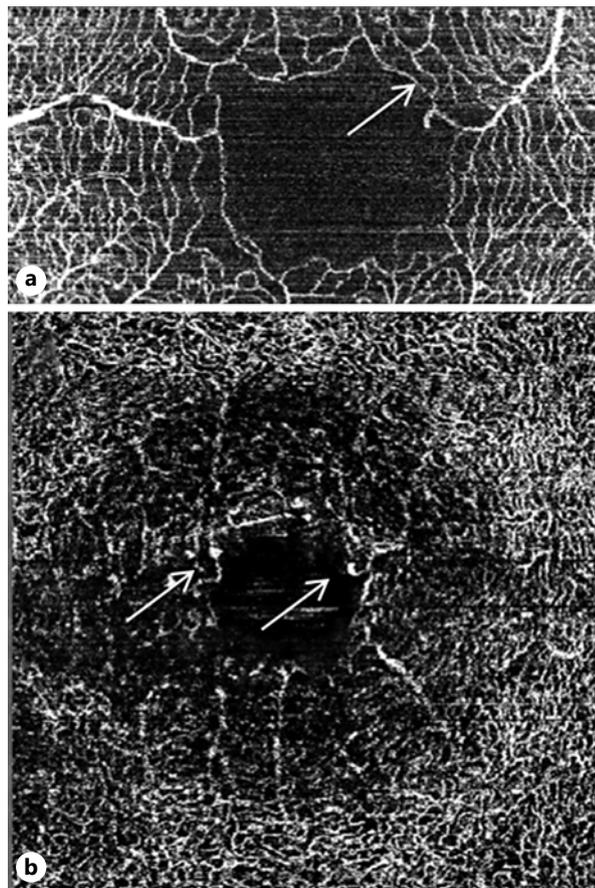


Fig. 3. OCT-A of DVLs of cases 1 (a) and 3 (b). Intercapillary distance appears increased in the near vicinity of the FAZ. Focal thickening of vascular flow signals (arrows) at the border of the FAZ suggests the presence of telangiectatic vessel abnormalities. DVL, deep retinal vessel layer.

Our study is limited by the small number of study patients that could be scanned and the moderate to poor image quality. However, since SLS is an extremely rare disorder and patients suffer from intellectual disability, spasticity, and photophobia, it is difficult and sometimes impossible to obtain high-quality OCT-A scans. Strength of this study is the fact that despite the small cohort, children as well as adults with different stages of SLS maculopathy could be included. Since all three stadia of SLS maculopathy were represented, yet showing similar vascular changes, this supports our idea of the possibility that vascular changes in SLS maculopathy are part of the pathophysiology. The healthy controls were all female adults; however, we do not think this influences our results since in the young adult category no differences between male and female eyes were seen in a previous study [14]. In comparison to a recent study by Zhang et al. [15] where healthy children were examined by OCT-A [15], our patients with SLS also showed significantly larger FAZ areas suitable with our assumption and there is an arrest in development in SLS. Our controls were not age-matched, but due to the considerable differences, we do not expect this to limit our study results. In summary, OCT-A showed low capillary density with a larger FAZ and abnormal vessel morphology in SLS.

Statement of Ethics

All procedures performed in the study were in accordance with the ethical standards of the Institutional Review Board/Ethics Committee at the Radboud University Medical Center and with the 1964 Helsinki Declaration and its later amendments. The “CMO Regio

Arnhem-Nijmegen” approved the study with reference number NL58544.091.16. Written informed consent was obtained from the parents/legal guardians of the patients (both children and adults’ since all patients have an intellectual impairment, they are not competent for signing themselves) for participation in the study and publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Pippa Staps: execution of the study, data analysis and interpretation, drafting of figures, and writing of the manuscript; Anita de Breuk: data analysis and interpretation and correction of the manuscript; Johannes R.M. Cruysberg: data interpretation and correction of the manuscript; Michèl Willemsen: data interpretation and correction of the manuscript; Thomas Theelen: conception and design of the study, data interpretation, and writing and correction of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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