Vitreomacular Interphase Disorders in Eyes with Proliferative Sickle Cell Retinopathy

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Authors’ contributions

This work was carried out in collaboration among all authors. Author O. Oderinlo designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AH and O. Okonkwo managed the analyses of the study. All authors read and approved the final manuscript.

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ABSTRACT

Purpose: To describe the type of vitreomacular interface disorders (VID) seen in eyes with proliferative sickle cell retinopathy, based on optical coherence tomography findings and assess their effect on visual acuity.

Patients and Methods: This was a retrospective observational case study. Clinical records and imaging records were reviewed to identify all PSR cases with Fourier-domain OCT imaging showing VIDs at a single academic private-practice office location from January 1, 2015 to July 30, 2018. Identified VIDs were classified as Vitreomacular Adhesions, Vitreomacular Traction, Lamellar Macula Hole, Full Thickness Macula Hole, Epiretina membranes and Macula Pseudohole.

Results: Out of a total of 98 eyes of 78 patients with PSR evaluated, only 12 eyes had VIDs; this represents 12.2% of PSR patients. There were 3 (25%) males and 9 (75%) females with ages ranging from 32 to 64 years, a mean age of 45.42yrs [SD 10.27], 9(75%) right eyes were affected. In 9(75%) patients their genotype was SC and 3(25%) with genotype SS. PSR was at stage 3 in 6(50%) eyes, while the remaining 6(eyes) were at stage 4. The most common VID was epiretina membranes (ERM) seen in 7(58.3%)eyes, in 2(16.6%) ERMs eyes were associated with Lamella Macula Holes and in 1(8.3%) the ERM was associated with a pseudohole. VMAs were seen in in 3(25%) eyes and FTMHs were seen in 2 (16.6%) eyes. ERMs were thus seen in 7.1% (7 eyes) of the 98 eyes with PSR that were considered.

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1. INTRODUCTION

Sickle cell retinopathy (SCR) is a series of characteristic retina complications that arise in patients with sickle cell haemoglobinopathy. The sickle cell haemoglobinopathies results from an abnormality in the beta chain of the haemoglobin molecule and the disease can be distinguished in sickle cell trait (Hb AS), sickle cell anaemia-homozygous sickle cell disease (SS disease), sickle cell disease-heterozygous sickle cell C disease (SC disease) and sickle cell thalassemia disease (S-thal disease). It is an autosomal incomplete dominant condition (inheritance is similar to recessive inheritance with one in four chance of SS if both parents AS). The S gene can have effects if combined with the C gene or thalassemia gene [1].

The gene is thought to have originated in West Africa where it is present in 10 to 14% of the population because of its relative protective effect on falciparum malaria (shorter living red blood cells and relative hypoxia may be detrimental to the malaria infection) [2]. The gene is also seen in eastern Mediterranean and Middle Eastern patients. SC disease is traditionally thought to develop more retinal complications, however, the complications are also seen in SS disease [3]. Most cases of retinopathy seem to appear between 20 and 40 years and stabilize or regress thereafter. This hereditary disorder causes the red blood cells to take on a sickle shape when under stressful conditions like in hypoxic states with the result of being rigid and passing with more difficulty through blood vessels, causing vascular occlusion in multiple organs including the retina with a number of clinical features in the eye [4,5].

Although many attempts have been made to classify the retina changes from sickle cell retinopathy, Goldberg’s 1971 [6] classifications still stands out as the most widely used. He classified sickle cell retinopathy into Proliferative and Non Proliferative. He further went on to classify the Proliferative type into 5 different stages. Stage 1 was Peripheral retinal arteriolar occlusion, stage 2 Arteriolar venular anastomosis seen at the junction of the perfused and non perfused retina, best seen on angiography, flat on the retina and non leaking. Stage 3 is characterized by neovascular proliferation in the retina periphery giving a ‘sea fan’ appearance, stage 4 Vitreous hemorrhage and stage 5 Retinal detachment usually tractional [5,6].

However Goldberg’s classic description made no mention of vitreomacula interphase disorders (VIDs) but with the advent of the Optical coherence Tomography (OCT) several vitreomacula interphase disorders (VID) have now been investigated in many retina diseases. Abnormalities of the VID are seen in other retinal pathologies such as diabetic retinopathy, diabetic macular edema and age-related macular degeneration. There is a paucity of information on VIDs in PSR. Eyes with VIDs can experience rapid deterioration in visual function if not managed in a timely and effective manner [7,8].

Traditionally visual loss from sickle cell retinopathy (SCR) is attributed mostly to complications of proliferative sickle cell retinopathy (PSR), in haemoglobin SC (HbSC) patients and cerebral vaso occlusive events in haemoglobin SS (HbSS) patients [9]. On cursory observation we see VIDs contribute to significant visual impairment in SCR patients. In this case series, we explore the different types of VIDs seen in patients with proliferative sickle cell retinopathy (PSR) and their effect on visual acuity. The following VIDs were included vitreomacular adhesion (VMA), vitreomacular traction (VMT), epiretinal membrane (ERM), full-thickness macular holes (FTMH), lamellar holes and pseudoholes.

The vitreous is considered central to the pathology of both PSR and VIDs [4,5,10,11]. Continuous tangential and antero posterior stretching on the macula can lead to VMT. In PSR recurrent bleeding into the vitreous encourages vitreoretina fibrosis, which eventually leads to a tractional retinal detachment, representing a progression from Goldberg stages 3 to 5 [10,11,12]. VMT can also lead to microscopic damage of the retinal surface especially in the region of the macular. The retina initiates a healing response, leading to a thin

**Conclusion:** Epiretina membranes with or without macular holes are the most common vitreomacular interphase disorders seen in our series of eyes with proliferative sickle cell retinopathy. They were associated with mild to moderate impairment in visual acuity.

**Keywords:** Vitreomacula interphase disorders; proliferative sickle cell retinopathy; macula hole; vitreomacula traction syndrome; vitreomacula adhesions; macula pseudohole.
layer of scar tissue and epiretinal membrane formation. Epiretina membrane tissue contains mostly fibrogial, thickened internal limiting membrane, astrocytes and myofibrocytes[13,14].

Over the past two decades, the role of vitreomacular adhesion in vitreomacular interface pathologies, have been increasingly recognized. There contribution to reduced vision has been evaluated in many retina pathologies like diabetic retinopathy, diabetic macular edema and age-related macular degeneration have also been recently reported [7,8]. There are however little information for VIDs in PSR. Our study reports the types of VIDs that are seen in PSR and how they affect visual acuity. This information will improve our knowledge of VIDs and help surgeons have a wider view of possible pathologies and considerations in decision-making.

**Purpose:** To study the type of vitreoretinal interface disorders (VID) seen in eyes with proliferative sickle cell retinopathy, based on optical coherence tomography findings and assess their influence on visual acuity.

**Study Design:** Retrospective observational study.

### 2. MATERIALS AND METHODS

This was a retrospective observational case study. Clinical records and imaging records were reviewed to identify all PSR cases with Fourier-domain OCT imaging showing VIDs at a single academic private-practice office location, (The Eye Foundation Hospital Lagos Nigeria) from January 1, 2015 to July 30, 2018. Patient demographics were expressed as frequencies and percentages and statistical analyses were performed using IBM SPSS Statistics Version 22 (IBM Corp. Armonk, NY, USA). All patients had their visual acuities taken with the snellen's visual acuity chart, anterior segment evaluation with the slit lamp biomicroscope, and intraocular pressure measurements by application tonometry and pupillary light reactions done. Fundoscopy with the indirect ophthalmoscopy as well as fundus photographs were done. Only patients newly diagnosed with proliferative sickle cell retinopathy and vitreomacular interphase disorders within the period of study were included. Patients with tractional retinal detachment; OCT strength signal index <0.0; previous vitrectomy, intravitreal steroids, previous laser treatment, dense vitreous hemorrhage precluding a view of the retina or any other previous intraocular surgery as well as any coexisting retinal diseases (including retinal vein occlusion and uveitis) were excluded from the study. The RTVue-100 OCT [Optovue Inc., Fremont, CA, USA] SD-OCT scan using a standardized protocol was used for all included images.

Identified VIDs were classified as Vitreomacula Adhesions (VMA), Vitreomacula Traction (VMT), Lamellar Macula Hole (LMH), Full Thickness Macula Hole (FTMH), Epiretina Membranes (ERM) and Macula Pseudohole. Vitreomacular adhesion (VMA) was defined as perifoveal vitreous separation with remaining vitreomacular attachment and unperturbed foveal morphologic features. Vitreomacular traction (VMT) was defined as anomalous posterior vitreous detachment accompanied by anatomic distortion of the fovea, which may include pseudocysts, macular schisis, cystoid macular edema, and subretinal fluid. A Full-thickness macular hole (FTMH) was defined as a foveal lesion with interruption of all retinal layers from the internal limiting membrane to the retinal pigment epithelium. A Lamellar macular hole (LMH) was defined as a partial thickness foveal defect with the presence of an intact photoreceptor base. Eyes with epiretina membranes and pseudohole formation were also identified. Our classification scheme for VIDs abnormalities was based on previously published classifications. [15] Visual acuities were classified using the ICO/Revised visual impairment definitions of the International Statistical Classification of Diseases [16] as follows 6/6 and better (Normal vision), 6/9 to 6/18 (Mild visual impairment), <6/18 to >6/60 (Moderate visual impairment).

### 3. RESULTS

Out of a total of 98 eyes of 78 patients with PSR evaluated, only 12 eyes had VIDs; this represents 12.2% of PSR patients. The patient demographics and clinical features of the 12 included eyes are summarized in Table 1. There were 3 (25%) males and 9 (75%) females with ages ranging from 32 to 64 years, a mean age of 45.42yrs [SD 10.27], 9(75%) right eyes were affected and 3(25%) left eyes. In 9(75%) patients their genotype was SC and 3(25%) had genotype SS.6(50%) eyes presented at PSR Goldberg stage 3, while the remaining 6(eyes) were at stage 4 (Table 1). Visual acuities ranged from 6/36 to 6/6, 5 (41.7%) eyes had normal vision (6/6 and better), 5 (41.7%) eyes had mild visual impairment (6/9 to 6/18), while the remaining 2 (16.6%) eyes had moderate visual impairment.
(<6/18 to >6/60) Table 2. The most common VID was ERM seen in 7(58.3%) eyes, in 2(16.6%) ERM eyes were associated with Lamella Macula Holes (LMH) and in 1(8.3%) the ERM was associated with a pseudohole. VMAs were seen in in 3(25%) eyes and FTMHs were seen in 2 (16.6%) eyes (Table 1). ERM were thus seen in 7(7.1%) eyes of the 98 eyes with PSR that were included in the study.

4. DISCUSSION

Epiretina membranes are the most common vitreoretina interface disorders seen in our series of eyes with PSR, 7(58.3%) eyes had ERMs, in 2(16.6%) eyes ERMs were associated with Lamella Macula Holes (LMH) and in 1(8.3%)eye the ERM was associated with a pseudohole. Hence 7.1% of eyes with PSR had ERMs in our series. Most eyes with epiretinal membranes in our series had mild visual impairment; visual acuity was 20/40 or better in 78.2% of eyes. In a study [17] that examined 769 patients (1486 eyes) with sickle cell disease from June 1978 to July 1985 for evidence of ERM, 51 eyes had macula and 4 eyes had extramacular region ERMs in the posterior pole. The incidence of epiretinal membranes, seen in the eyes of patients with hemoglobin SC, SS, and SB+ thalassemia, was 3.7% [17]. The incidence of ERM in our study is thus almost double this previous report at 7.1% of eyes. This difference may be associated with the use of the OCT as the main diagnostic tool in our study when compared to the slit lamp and fundus photographs. OCT is a non-invasive diagnostic tool that has revolutionized the diagnosis of vitreomacula interface disorders. Findings of VMTs, VMAs are easily made with the OCT. Duker et al [15] in their article reveal a new classification of VIDs based on OCT findings, prior to this tool diagnosis like, VMA were difficult to make.

VMAs were the second most common VIDs seen in our series of patients with PSR. VMAs were seen in 3(25%) eyes with VIDs. VMA is a perifoveal vitreous detachment and is the equivalent of a stage 1 PVD these changes are thought to have occurred since birth and represents a specific stage of vitreous separation wherein partial detachment of the vitreous in the perifoveal area has occurred, without retinal abnormalities [18,19].

Table 1. Table showing demographic data of patients, presenting visual acuity and type of vitreoretina interphase disorders in eyes with proliferative sickle cell retinopathy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Eye</th>
<th>Genotype</th>
<th>VA (Best corrected)</th>
<th>Stage of PSR</th>
<th>Vitreoretina interphase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43</td>
<td>F</td>
<td>RE</td>
<td>SC</td>
<td>6/9</td>
<td>4</td>
<td>ERM</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>F</td>
<td>RE</td>
<td>SS</td>
<td>6/24</td>
<td>3</td>
<td>FTMH</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>F</td>
<td>LE</td>
<td>SC</td>
<td>6/6</td>
<td>3</td>
<td>ERM</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>F</td>
<td>RE</td>
<td>SC</td>
<td>6/9</td>
<td>4</td>
<td>Focal VMA</td>
</tr>
<tr>
<td>5</td>
<td>38</td>
<td>F</td>
<td>RE</td>
<td>SC</td>
<td>6/9</td>
<td>4</td>
<td>Broad VMA</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>M</td>
<td>RE</td>
<td>SC</td>
<td>6/5</td>
<td>4</td>
<td>ERM</td>
</tr>
<tr>
<td>7</td>
<td>36</td>
<td>F</td>
<td>RE</td>
<td>SC</td>
<td>6/36</td>
<td>3</td>
<td>FTMH</td>
</tr>
<tr>
<td>8</td>
<td>64</td>
<td>F</td>
<td>RE</td>
<td>SS</td>
<td>6/18</td>
<td>3</td>
<td>ERM+LMH</td>
</tr>
<tr>
<td>9</td>
<td>43</td>
<td>F</td>
<td>RE</td>
<td>SS</td>
<td>6/12</td>
<td>3</td>
<td>ERM+LMH</td>
</tr>
<tr>
<td>10</td>
<td>49</td>
<td>F</td>
<td>LE</td>
<td>SC</td>
<td>6/6</td>
<td>4</td>
<td>Broad VMA</td>
</tr>
<tr>
<td>11</td>
<td>52</td>
<td>M</td>
<td>RE</td>
<td>SC</td>
<td>6/6</td>
<td>4</td>
<td>ERM+Pseudohole</td>
</tr>
<tr>
<td>12</td>
<td>32</td>
<td>M</td>
<td>LE</td>
<td>SC</td>
<td>6/6</td>
<td>3</td>
<td>ERM</td>
</tr>
</tbody>
</table>

Table 2. Table showing visual acuity categories for different types of vitreomacula interphase disorders in eyes with proliferative sickle cell retinopathy

<table>
<thead>
<tr>
<th>Visual acuity group</th>
<th>FTMH</th>
<th>ERM+LMH</th>
<th>VMA</th>
<th>ERM</th>
<th>ERM + Pseudohole</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/6 and better (Normal vision)</td>
<td>-</td>
<td>-</td>
<td>1(8.3%)</td>
<td>3(25%)</td>
<td>1(8.3%)</td>
</tr>
<tr>
<td>6/9 to 6/18 (Mild visual impairment)</td>
<td>-</td>
<td>2(16.6%)</td>
<td>2(16.6%)</td>
<td>1(8.3%)</td>
<td>-</td>
</tr>
<tr>
<td>&lt;6/18 to &gt;6/60 (Moderate visual impairment)</td>
<td>2(16.6%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Total | 2(16.6%) | 2(16.6%) | 3(25%) | 4(33.3%) | 1(8.3%) |
Full thickness macula holes were seen in 2 (16.6%) eyes and LMH in 2 (16.6%) eyes. Macular holes are reported rare in sickle cell retinopathy. In a study of 500 sickle cell patients, Raichand et al. [20] found 4 (0.8%) eyes with macular holes. All cases showed evidence of peripheral PSR and the two LMH had epiretinal membranes that caused traction on the macula, they had SC-type disease, PSR, and epipapillary fibroglial tissue proliferation, and none had undergone photocoagulation treatment. The proposed mechanism of hole formation is related to contraction of the epiretina membranes. Another possible mechanism of macular hole formation may be occlusion of perifoveal capillaries with consequent local ischemia that leads to retinal atrophy, thinning, and hole formation [20]. This reported incidence of 0.8% is much lower than 2.04% in our series of patients. Fig. 2 shows the eye with a full thickness macula hole and associated fibrovascular tissues in the superior vascular arcade. Eyes with a FTMH had moderate visual impairment with a vision of 6/36 (Table 2), 5 (41.5%) eyes had only mild visual impairment and the remaining 5 (41.5%) had normal vision. Hence despite ERMs, VMAs, VMTs and even macula pseudohole formation, visual acuity can still remain normal. This helps us to know that visual acuity alone is not the best way to screen for VIDs. The OCT is a better tool for evaluating for VIDs. With the use of the OCT, better definition of macula changes can be done. The OCT was initially introduced using the Time Domain (TD-OCT) imaging technique, based on a detection technique that uses a low-coherent light source and a changing focus point to generate the A-scan data. Over subsequent years several improvements have been made in the technology. By the end of the 1990’s, technology moved to a new technique called Fourier Domain (Spectral Domain), which greatly improved sensitivity and allowed a dramatic reduction in scan time by capturing the complete A-scan data relative to a single focus point in the sample. The OCT employed in our study uses the Fourier Domain technology and gives higher resolution images when compared to the initial Time Domain (Figs. 1 and 2).

In order to avoid reporting the complications of treatment, only treatment naive eyes were included in our study. All previous laser photocoagulation, vitrectomy, intravitreal antivegf or steroid treated eyes were excluded. The retrospective design is a limitation as only findings recorded in case files and images

Fig. 1. OCT AND fundus picture of the right eye of patient 8 (64 year old female with genotype SS) showing epiretina membrane formation and Lamellar macula hole
captured on OCT were evaluated. The possibility of evaluating any other changes in the vitreoretina interphase was thus unlikely. Retinal detachment for instance has been reported. Schuber [21] reported two cases of retinoschisis in sickle cell disease patients and Raichand [20] described a single case of retinoschisis in a series of 500 patients. The schisis is related to chronic low-grade ischemia of the inner nuclear layer, which houses the Müller cells, the structural backbone of the retina [22]. However, in our series of patients we did not see any patient with retinoschisis. Proliferative sickle cell retinopathy was mostly at stage 3 (50%) and 4 (50%) by Golbergs classification [6], those at stage 4 only had early vitreous hemorrhage. Patients with dense vitreous hemorrhage precluding a view of the retina were excluded because an OCT could not be performed.

In view of the small number of cases in this study, our results are preliminary and we expect it will stimulate further studies on the topic. Larger studies and possibly longitudinal designs are needed to better understand the effect of different types of VIDs on visual acuity in eyes with PSR.

The role of the vitreomacular interface (VMI) in the retina cannot be over emphasized. From VMA to VMTs, MHs and ERMs, understanding its role in the emergence and development of several retinal diseases is important. In PSR patients, the VMI can significantly influence the emergence, progression, and response to treatment. Further understanding of the VMI in PSR is warranted in order to better design imaging techniques and treatments to arrest and possibly even reverse progression of PSR and VMI, thus avoiding unnecessary blindness.

5. CONCLUSION

Epiretina membranes with or without macular holes are the most common vitreomacular interphase disorders seen in our series of eyes with proliferative sickle cell retinopathy. They were associated with mild to moderate impairment in visual acuity.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard written ethical permission has been collected and preserved by the authors.
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COMPETING INTERESTS
Authors have declared that no competing interests exist.

REFERENCES