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Familial Phenotypic Spectrum of Reis-Bücklers Corneal Dystrophy: A Rare Case

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ABSTRACT

Reis-Bücklers corneal dystrophy (RCBD) is a rare, bilateral and autosomal dominant inherited disease that primarily affects superficial corneal layers. It is generally accepted that a mutated TGF-β1 induced protein accumulated in this type of dystophy, but the exact pathophysiological mechanism remains unrevealed.This article aims to report a case of an Indonesian family with Reis-Bücklers corneal dystrophy.Case Illustration shows thirthysix yearold Indonesian male with a complaint of white patches on the cornea for both eyes, accompanied with foreignbody sensation, and blurred vision since young age. At that time of examination, the best corrected visual acuity was 1/60 (OD) and hand movement (OS). Slit-lamp examination of the both eyes revealed geographic opacification on central cornea for both eyes. The same characteristics also found in his siblings, as well as his child. There were various phenotypes severity for each patient based on age of onset. All cases were diagnosed with Reis-Bücklers corneal dystrophy.RCBD diagnosed by its typical clinical features, its unique opacities affect the bowman's layer and superficial corneal stroma. We reported rare cases of an Indonesian family with typical phenotype trait of RCBD inherited autosomal dominantly, with the specific clinical appreance were opacities that reach the bowman's layes and some stormal layer of the cornea that tend to worsen by aging and normal endothelial cell density on microscopic specular. The dystrophic corneas were thicker than normal, the value of pediatric patientscorneal thickness less than the adults.

Keywords: corneal dystrophies, reis buckler, indonesian family

INTRODUCTION

Corneal dystrophies are rare and usually autosomal dominant genetic disorders with bilateral, symmetrical, and non-inflammatory progressive corneal opacities that lead to varying degrees of visual impairment. Although they are rare, the corneal dystrophies are phenotypically complex with the involvement of one or more of the five distinctive corneal layers and they have an extensive eponymous classification. CDs were classified based on clinical manifestation, pathologic examinations, and genetic data referred to International Committee for Classification of Corneal Dystrophies (IC3D), edition 2. Depending on IC3D classification, there are four types of corneal dystrophies: epithelial and subepithelial dystrophies, ephitelial-stromal dystrophies, stromal dystrophies, and endothelial dystrophies. s. Majority type of CDs are inherited as autosomal dominant with a mutation in the Transforming Growth Factor Beta Induced (TGFBI) gene. The TGFBIgene, located at chromosome 5q31.1, contains 17 exons and encodes a 683-amino acid extra-cellular matrix protein (TGFBIp) with a molecular weight of 68kDa, which is expressed in the cornea and other tissues (Shuetal., 2015; Weissetal., 2015; Xiangetal., 2019; Zhangetal., 2019).

Reis-Bucklers corneal dystrophy (RBCD) is an inherited corneal disorder that was first described by Reis in 1917 and later by Bucklers in 1949. Affected individuals have an onset early in life and have frequently recurring, painful corneal erosions, superficial corneal opacities, and significant visual impairment. Genetically, RBCD inherited in an autosomal dominant pattern. To date, the Arg124Leu mutation of transforming growth factor induced gene

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(TGFBI, protein: TGFBIp, or keratoepithelin) was the only mutation detected in the serum DNA from patients with RBCD. Can be confused with Thiel-Behnke corneal dystrophy (TBCD) especially in the first 2 decades. In this early stage, RBCD shows more irregular diffuse opacities with clear interruptions, whereas TBCD exhibits multiple flecks with reticular formation (Tanhehcoetal., 2006; Qiuetal., 2016; Zhangetal., 2019).

Reis-Bucklers corneal dystrophy tends to cause more extensive corneal opacities, more severe visual impairment, and a higher frequency of recurrence compared with TCBD. Because the clinical phenotypes of RBCD and TBD are similar (especially in young individuals), an accurate distinction between the 2 disorders necessitates either a microscopical examination of corneal tissue or a molecular genetic analysis. RBCD affects primarily Bowman's layer with the presence of band shaped granular and subepithelial deposits that begin to appear during the first or second decade of life. Although it is generally accepted that a mutated transforming growth factor-β-induced protein accumulated in RBCD, its exact patho physiological mechanism remains unknown. Clinically, Reis–Bücklerscor- neal dystrophy is characterized by confluent geographic opacities whereas Thiel-Behnke corneal dystrophy by honeycomb-shaped opacities. Microscopically, RBCD is characterized by confluent opacities in the Bowman layer and the subepithelium. Because the slitlamp cannot provide details of corneal structures at the cellular level, many corneal dystrophies and most particularly granular dystrophies are difficult to distinguish. Recently developed in vivo imaging techniques such as in vivo confocal microscopy (IVCM) and anterior segment (AS) optical coherence tomography (OCT) are providing new insights into the clinical evaluation of corneal dystrophies. Advanced cases of RBCD, a superficial keratectomy, phototherapeutic keratectomy (PTK) or lamellar keratoplasty (LKP) may improve vision, but a penetrating keratoplasty (PK) is rarely necessary because the pathologic changes only involve the superficial cornea(Qiuetal., 2016; Tanhehco et al., 2006; Liang etal., 2014; Lisch&Weiss, 2019).

CASE REPORT

Patient 1. A 36-year-old male came to the outpatient ophthalmology clinic in AXIS Makassar, complained of white patches on the cornea for both eyes, sometimes irritated, and blurred vision since young. He felt his eyesight become even more blurred. Best corrected visual acuity was 1/60 in the right eye (RE) and hand movement in the left eye (LE). Eye examination revealed irregular granular like epithelial until stromal gray-white opacities were observed in the central and peripheral cornea with yellowish plague in both eyes. The patient corneal thickness was 523um on the right eye and 580um on the left. Further history taking, revealed some of his family members have the same eye conditions as well and he this patient alredy done some treatment for his eye.

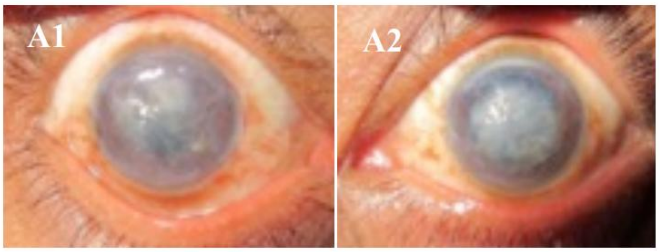

Fig 1. Clinical photographs of the first patients.A1 and A2 showed prominent irregular gray-white opacities in central to pheripheral of cornea.

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Patient 2. A 24-year-old male, brother of patient 1 with futher history taking, complained of withish on the anteior segment of the eye and blurred vision realized since elementary school. At the time of the examination, the best corrected visual acuity was 20/200 for both eye, the corenalthickness 703um (RE) and 603 (LE), no history of red eye, trauma and using spectacles. Slitlamp examination revealed the same confluent irregular, geographic-like opacities, with milder phenotype appearance. On direct questioining, he did state sometimes he bothered by glare.

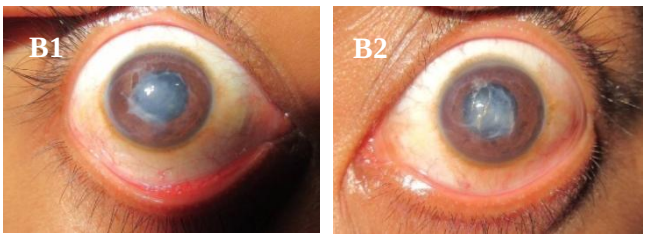

Fig 2. Images of the cornea of the second family mamber of the first patient with RBCD.The B1 and B2 cornea in both eyes showed gray-white opacities with more milder opacities on the central of the conrea and a clear peripheral cornea area.

Patient 3. A-14-year-old female, daugther of patient 1, were brought by her father to be examined as well. She was asymptomatic. She had no history of ocular trauma, infection and inflamation, no history of using spectacles and had no history of opthalmic examination before. Her parents realized that the anterior segment of their daughter eyes are white since the child was in elementary school She had the BCVA of 20/100 in the right eye and 20/60 in the left eye. The corenal thickness were 630 um (RE) and 655 (LE). Direct examination revealed smaller deposits and geographic opacities scattered in central of cornea compared the peripheral on both eyes. However, the density of the corneal opacities was lower in the daughter than in her father.

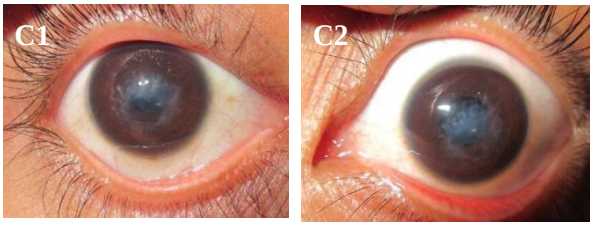

Fig 3. Images of the corneas of the daughter with RBCD: (C1&C2) Greyish-white geographic like opacities of the right and left eye. The cornea between the opacities and the peripheral cornea appeared transparant.

Patient 4. A-9-year-old male, son of patient 1 also came and examined. He was sometimes complained irritated eyes. There was a no history using spectacles. Corrected distance visual acuity was 20/50 in right eye and 20/60 in the left eye. The corenal thickness were 630um (RE) and 597 (LE). Direct examination revealed irregular geographic like subepithelial gray-white opacities were observed in the central and midperipheral corneas of both eyes. There was no sign of infection, inflamation and other ocular abnormalities. Slit-lamp biomicroscopy revealed there are bilaterally corneal opacity. The opacities were diffuse gray-white sand like in confluent or non-confluent geographic morphology with a normal conealperipherally.

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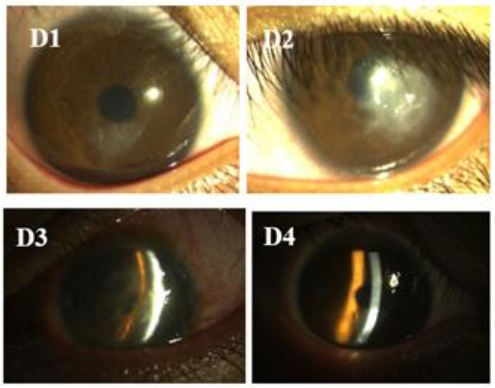

Fig 4. Direct examination photograps of patients the cornea of patient 4, showed geographical like opacities in smaller size and scattered in the central of cornea. D3 and D4 the cornea of right and left eye from the slitlamp examination showed opacities in epithelium reaching stroma.

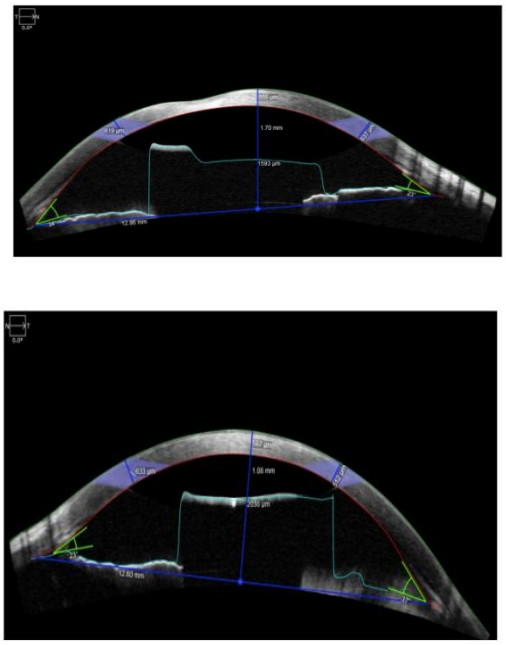

Fig5. Male patient (9 years). High-resolution corneal scan with domain OCT. There is increased reflectivity form epithelium until the stroma layer of the cornea. The areas of increased stromal reflectivity correspond with corneal opacities. The dystrophic material became thinner in the peripheral cornea and disappeared before the limbus.

DISCUSSION

Reis-Bücklers corneal dystrophy is a rare, bilateral and autosomal dominant inherited disease that primarily affects Bowman's layer. As evidence, if we search for atricle or lilerature on online search engines, for example Pubmed, only 11 article or research will appear in the last 5 years. The prevalence of corneal dystrophies is unknown, but all are rare and found mainly in populations containing the responsible mutated gene. Confluent early irregular geographic-like opacities with varying densities develop at the level of the Bowman layer and superficial stroma, initially discrete and subsequently extending to the limbus and deeper stroma. Their vision is impaired from childhood. The diagnosis of Reis-Bücklers corneal dystrophy can based on the clinical presentation, although several articlesuggest to correlate the clinicopathological. Genetically, RBCD inherited in an autosomal dominant pattern. To date, the Arg124Leu mutation of transforming growth factor induced gene (TGFBI, protein: TGFBIp, or keratoepithelin) was the only mutation detected in the serum DNA from patients with RBCD.

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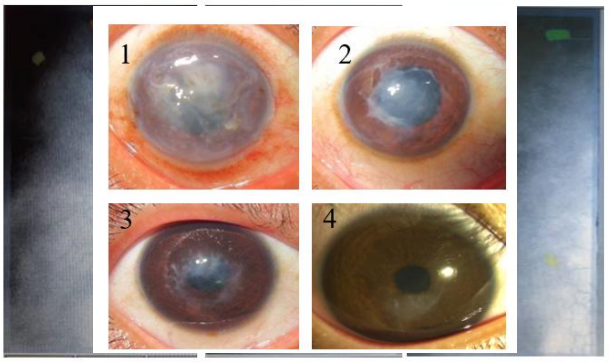
The surgical treatment indicated when the corneal deposits significantly decrease visual acuity and when painful corneal erosions recur despite medical therapies consisting of cycloplegic drops, antibiotic ointment, and bandage contact lens placement (Tanhehcoetal., 2006;Qiuetal., 2016; Gulias-Canizoetal., 2006; Lisch, &Weiss, 2019).

In this case report, all subjects received detailed clinical examinations including visual acuity, slit lamp biomicroscopy, microscopic specular and optical biomtery. We found that there are typically phenotypes characteristics in four patients of the family: the proband's (II-F), the brother (II-G), the daughter (III-E) and son (III-F). All of the patient realized the anterior segment of their eye became whitish since elemantary school. Slit-lamp biomicroscopy revealed there are bilaterally, asymmetric, the progressive corneal opacities more severe in the oldest patient in the family. Based on slit-lamp examination, we found typical manifestation as gray-white geographic opacity in the anterior to stroma of both eyes. In two pediatric patients, the proband's child (III-E, 14-year-old, and III-F, 9-year-old) with visual acuity equal or more than 20/100, the corneal opacities in non-confluent geographic morphology were found. The clinical features were found, including developing opacities of the Bowman's layer, were consistent with the characteristic of RBCD. The degrees of phenotypes severity seemed to be age-dependent.

The cilinical manifestation in the proband (II-F), we found more severe phenotype appearance compared with the youngest patient (III-F) epthelial-stromal layer. The central corneal thicness evaluated by using aladdin biometry, we found the dystrophic corneal were thicher than normal, and the pediatric patient coneal thickness value thinner than the adults, except the first patient. Based on the clinical features, the family was preliminarily diagnosed as having Reis-Bücklers corneal dystrophy.

Fig 6. Different phenotypes appereance in various age spectrum of the family member. 1.Proband (IIF), severe phenotype. Moderate phenotypes in Patient 2(IIG). Mild phenotype in patient 3(IIIE) dan 4(IIIF).



Phenotypically, the pedigree we documented here exhibited typical features of RBCD. The affected individuals presented with a gray-white geographic opacity in the anterior to mid-stroma of both eyes. The results from the history taking, clinical examination and other phenotypic test correlating with the Reis-Bücklers corneal dystrophy trait that leads to be inherited autosomal dominantly. In addition, geometric and round opacities in the subepithelial layers and anterior to stroma were found in all of the affected family members. Further routine ophthalmic examination on the patient is required. The results from the history taking and phenotypic test correlating with the reis-buckler corneal dystrophy trait that is inherited autosomal dominantly. In addition, microscopic specular examination has been performed on

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these patients, and it shows normal endothelial cell density for both eye of all patients, without polymegathism and pleomorphism findings as seen on the figure 6. Several study suggest to examine the genetic analyses which provide a precise diagnosis. Although the advance cases RCBD suggested to treated with PTK or keratoplasty, the donor availibilty was the major obtacles at this era. Because of that the low vision consultation should be considered as a choice in advance RCBD.

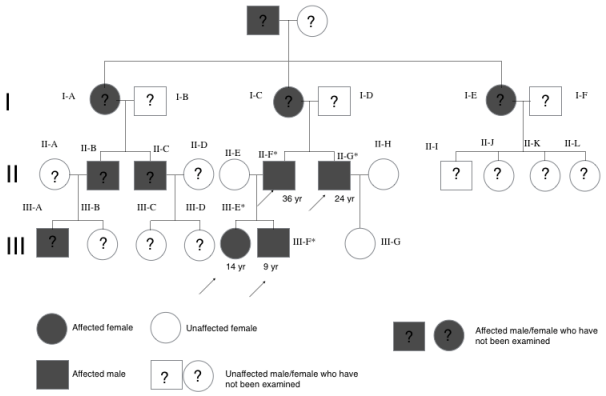

Fig 8. Pedigree of the Family Suffered from Reis-Bücklers corneal dystrophy

CONCLUSION

This case showed typical clinical manifestations correlating with phenotype characteristics in a family according to the disease's progression thus the severity of the phenotype is age-dependent. It can be can be challenging to determine a clinical diagnosis solely on phenotype characteristic, especially in mild cases or in a case with no phenotype findings yet. From this case report, a suggestion to do prospective genetic screening in relatives may be important and long-term observation is needed. And comprehensive examination was really important to differentiate each corneal distrophies identification and to rule out possibilities and confirm a final diagnosis. Be short of because of the pandemic other family member mentionend by the subject that we evaluated postpone to investigate.

The equation of the clinical examination we found in this case report and a study in 2010 of Reis Bukler in a four-generation Chinese family from China is the slit lamp examination showed multiple annular grayish opacities at the subepithelial and anterior stroma of the central cornea of both eyes. In addition, patients with older age from both cases have progressive vision loss and their corneal opacity recognized since the young age. The younger patient from those study presented with no clinical symptoms, same condition that we found in our patients (Maetal., 2010).

In another examination we did, AS OCT, reavealed hyperreflective homogeneous and continuous deposits concentrated at the level of the Bowman's layer and stroma, this was also found in a study at the Beijing Institute of Ophthalmology in 2014, in which they characterized the phenotype of Reis-Bücklers corneal dystrophy (RBCD) using in vivo and ex vivo imaging technology. The biometric also revealed the central corneal thicness tend to thicker in RBCD patient (Qiuetal., 2016). These findings will expand the knowledge about Reis–Bücklers and demonstrate that molecular genetic analysis is also important to make an accurate diagnosis of patients with corneal dystrophies.

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