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ANATOMICAL CHANGES BETWEEN ARGUS II RETINAL PROSTHESIS AND INNER RETINAL LAYERS DETECTED BY SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY IN FIRST YEAR: A CASE REPORT

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Purpose: To report and describe the anatomical changes detected by spectral domain optical coherence tomography between an Argus II retinal prosthesis and the inner retinal layers during 1-year follow-up.

Methods and Results: A patient presented with epiretinal fibrosis 12 months after implant of an Argus II epiretinal prosthesis. One month after uneventful surgery in March 2016, an evident hyporeflective space was detected between the epiretinal prosthesis and the inner retinal surface by spectral domain optical coherence tomography. An epiretinal hyperreflective band was noticed during follow-up and 1 year after surgery. Spectral domain optical coherence tomography showed close contact of the band with the array, which greatly increased the electrical threshold of stimulation for most of the electrodes. Some electrodes were no longer functioning. No changes in visual performance were detected.

Conclusion: Argus II epiretinal prosthesis implant may be complicated by the formation of a hyperreflective epiretinal band, detectable by spectral domain optical coherence tomography. The band may alter prosthesis function; to date, the patient did not scored any decrease in visual function.

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The Argus II retinal prosthesis system (Second Sight Medical Products, Inc, Sylmar, CA) is a commercially available surgically implantable epiretinal device designed to provide artificial vision to patients with late-stage outer retinal degenerative disease, such as retinitis pigmentosa, as described by da Cruz et al[1] and Rizzo et al.[2] It consists of an external video-processing unit that translates visual information from an eyeglass-mounted video camera into electrical signals. The implanted part consists of a receiver coil that sends electrical stimuli through a polymerized cable to a 60-electrode array implanted on the retinal surface and fixed using a retinal tack. Electrical stimulation of the inner retina evokes action potentials that travel through the optic nerve to the brain and elicit visual percepts. The device has been implanted in more than 250 patients worldwide since it was commercially approved in the European Union (CE Mark) in March 2011 and by the US Food and Drug Administration (FDA) in February 2013.

Case Report

A 52-year-old patient with an autosomal recessive form of retinitis pigmentosa was implanted with an Argus II in March 2016. In 1992, he was referred to the retinal dystrophies service of ASST *Santi Paolo e Carlo* University Hospital in Milan, Italy, with right

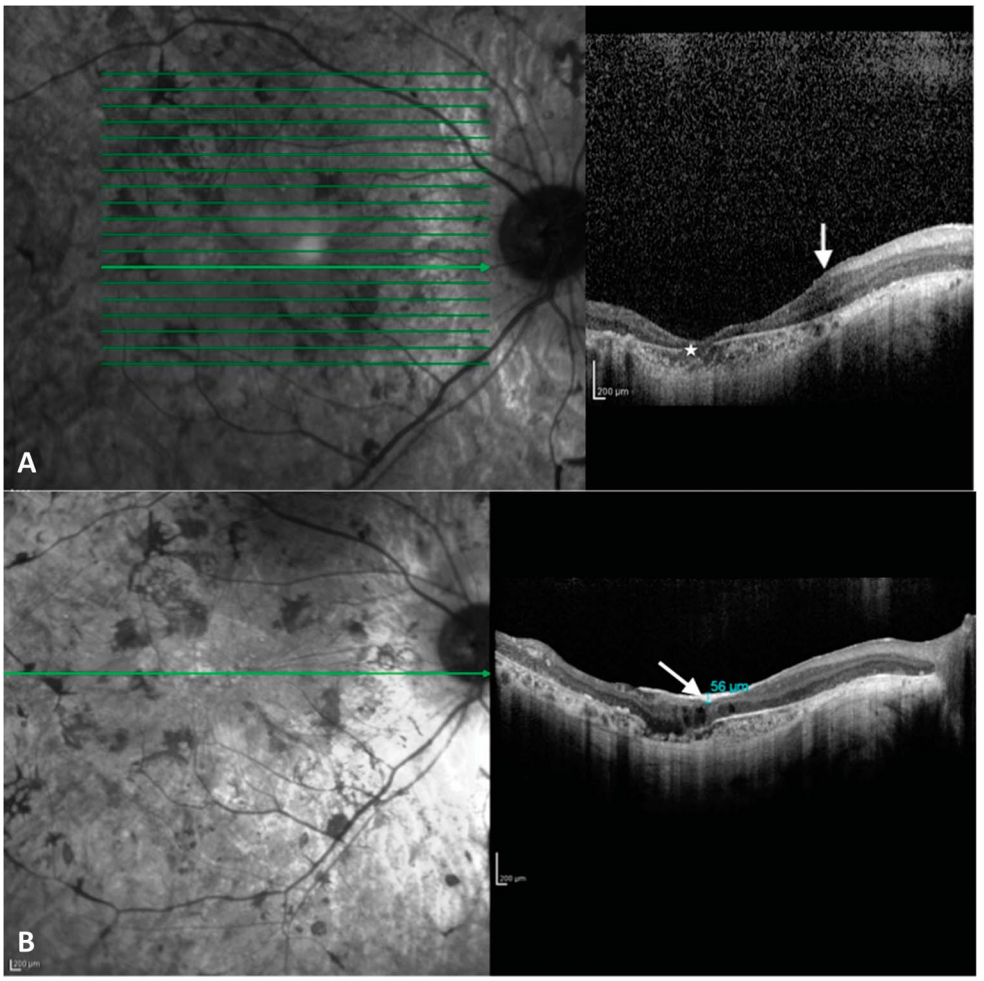

Fig. 1. Preoperative horizontal SD-OCT scan of the macula. In 2011, (**A**) outer retinal layers were completely atrophic and focally involved the retinal pigment epithelium and choroid (star). No ellipsoid zone band was detectable. The inner retina showed slight thickening of the internal limiting membrane (arrow). In 2015, (**B**) hyperreflective epiretinal fibrosis became more evident (arrow) and retinal thickness increased.

eye best distance-corrected visual acuity 20/200 and left eye 20/32 and severely reduced central and peripheral visual fields. After progressive visual impairment, visual acuity was no light perception in both eyes in 2006, 10 years before surgery.

Before surgery, the patient underwent complete ophthalmic evaluation. Spectral domain optical coherence tomography (SD-OCT) showed slight posterior staphyloma, which was not considered a contraindication for surgery, and a thin, adherent hyperreflective epiretinal membrane that increased slightly in thickness in the 5 years before surgery (Figure 1). Because visual acuity was no light perception, conduction of the optic nerve was tested by transpalpebral electrical stimulation to elicit phosphenes.

In March 2016, an Argus II device was successfully implanted by the vitreoretinal team. The thin epiretinal membrane was not removed to avoid damaging the fiber layer. No postoperative complications were observed at scheduled follow-ups after surgery.

Anatomical and Functional Follow-up

One Month

At 1-month postoperative follow-up, SD-OCT showed the device in place and in contact with the retina in the area of the tack. In the macular area, SD-OCT detected a hyporeflective space between the device and the inner retina. The maximum distance between the array and the inner surface of the retina at the macula was 235 μm (Figure 2A). The device was tested, and the fitting procedure was performed; the results are reported in Figure 3A. The 60 electrodes of the array were classified as follows: Group 1 if phosphenes were elicited by 0 μA to 234 μA (low threshold), Group 2, 235 μA to 452 μA (medium threshold), Group 3, 453 μA to 677 μA (high threshold), and Group 4, if no phosphenes were elicited in any of the 3 ranges of stimulation. We found 46/60 electrodes in Group 1, 8/60

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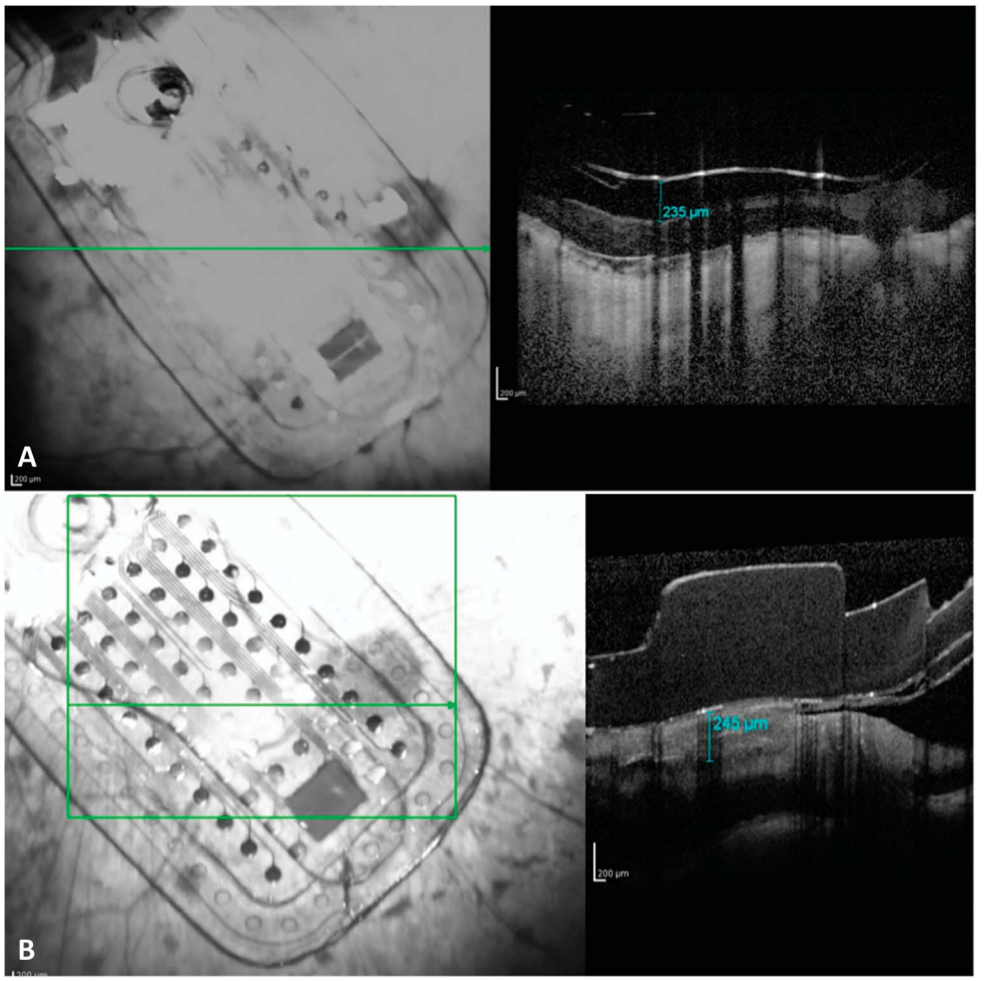

Fig. 2. Postoperative horizontal SD-OCT scan of the macula. One month after surgery, (**A**) the array was separated from the inner surface of the retina by a hyporeflective space: maximum distance 235 μm. One year after surgery, (**B**) retinal thickness was much greater and a thick hyperreflective band was clearly visible between the array and the inner surface of the retina. The array was in close contact with the epiretinal fibrosis. Maximum thickness of the fibrosis was 245 μm.

in Group 2, 1/60 in Group 3, and 1/60 in Group 4; 4/60 electrodes were no longer functioning.

One Year

At 1-year post-operative follow-up, SD-OCT showed the device in place. Spectral domain OCT scans of the macular region showed a remarkable increase in retinal thickness and a thick hyperreflective band that filled the space between the device and the inner retina. The maximum thickness of the hyperreflective band was 245 μm (Figure 2B). We repeated the fitting process to determine the impact of these changes on electrode thresholds. We noted that some electrodes in close contact with the epiretinal hyperreflective tissue were no longer functioning, while the electrical threshold of others was much higher than recorded at 1-month follow-up. The results of fitting 1 year after surgery are reported in Figure 3B: 15/60 electrodes were classified in Group 1, 10/60 in Group 2, 21/60 in Group 3, and 8/60 in Group 4; 5/60 electrodes were no longer functioning.

Despite this decrease in electrode function, the patient did not notice any decrease in visual function and scored very well-identifying letters, words, and objects on a black screen.

The other eye was used as control. Over the period of follow-up, SD-OCT of the other eye showed a slight increase in the hyperreflective epiretinal membrane and in central macular thickness (Figure 4).

Discussion

In this report, we describe a major increase in epiretinal fibrosis between the intraocular array of the Argus II epiretinal prosthesis and the inner surface of the retina over the period of 1 year. SD-OCT scan of the macular area was performed for the first time in 2011 and slight thickening of internal limiting membrane was detected. The thickness of the epiretinal membrane subsequently grew very slowly until implant of the array, after which it increased dramatically in the course of a year. Because the other eye did not show any significant change, it

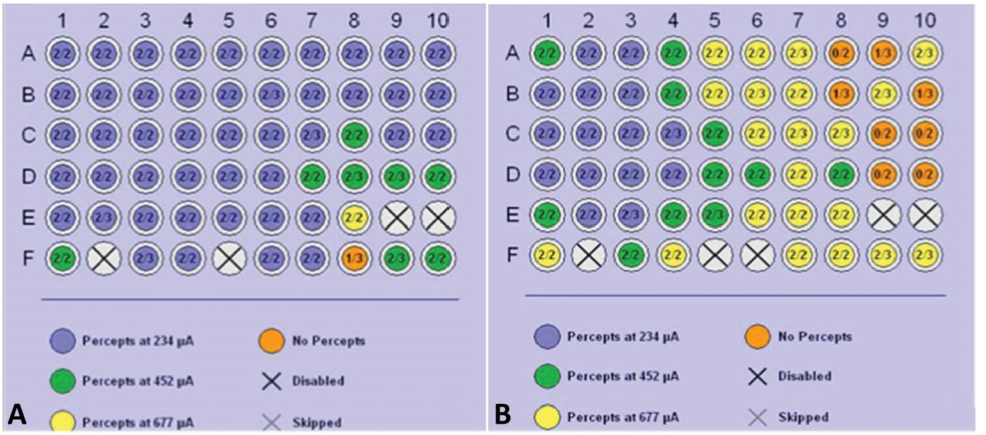

Fig. 3. Schematic representation of Argus II device electrical threshold. Colors represent the group each electrode belong to. Violet = Group 1, green = Group 2, yellow = Group 3, orange = Group 4. The electrodes represented with a cross-mark were disabled. Results of the fitting process 1 month after surgery (**A**) and 1 year after surgery (**B**) are shown.

seems likely that the device played a role in the thickening process.

It is well-known from previous studies, such as De Balthasar et al[3] and Ahuja et al,[4] that there is a significant correlation between the electrical threshold needed to elicit phosphenes and the distance between the electrodes and the retina. As described above and as clearly visible in Figure 2A at the time of the first fitting (1-month postoperative), the array was not in direct contact with the inner surface of the retina. Notwithstanding this, most of the electrodes were classified in Group 1 (low current), so that the fact that, in our case, the array was not in direct contact with the inner part of the retina does not by itself explain this change.

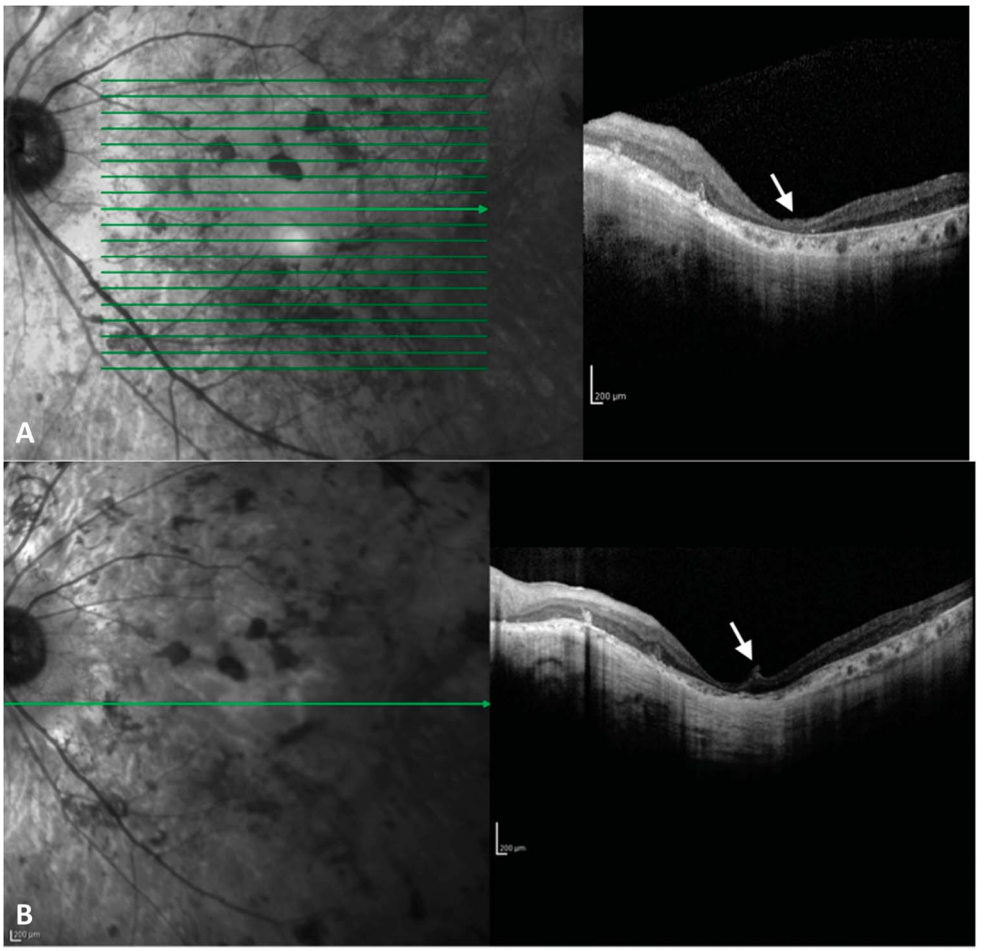

Fig. 4. Horizontal SD-OCT scan of the macula of the other eye. In 2011, (**A**) the outer retinal layers were completely atrophic, and no ellipsoid zone band was detectable. The inner retina showed slight thickening of the internal limiting membrane (arrow). In 2015, (**B**) localized traction became evident (arrow) and retinal thickness increased focally.

Since 2004, when Chow et al[5] suggested the effects of electrical stimulation on retinal functions and activities, many groups have investigated the topic, and numerous studies in vitro and in vivo have demonstrated that electrical stimulation of the retina upregulates expression of neurotrophic factors, such as endogenous insulin-like growth factor and fibroblast growth factor 2, and of proteins involved in cell signaling, neurotransmission, and metabolic, immunological, and structural functions, as reported by Sehic et al.[6] This suggests that chronic stimulation of the retina may induce local biochemical changes and could play a role in the rapid growth of preexisting epiretinal fibrosis.

Another hypothesis is that slight movements of the array could determine repetitive extensive contact with the retina. This mechanical rubbing between the device and the retina could cause chronic inflammation that could somehow contribute to the proliferation of fibrotic tissue.

The fitting procedure repeated 1 year after surgery showed that some electrodes were no longer functioning, and others needed a higher electrical current to elicit phosphenes. Analyzing the array scans topographically, we observed that the most significant variations occurred in electrodes overlying the thickest part of the fibrosis. The distance of the array from the retina therefore presumably influences the electrical threshold, while fibrosis of the epiretinal membrane also presumably limits conductivity.

In our case, a hyperreflective epiretinal membrane was clearly detectable by SD-OCT before surgery and is likely to have acted as a substrate for other factors in the pathogenesis of postoperative fibrosis. The possibility of removing the internal limiting membrane and epiretinal membrane during implant surgery should be considered as a way to prevent future growth of the epiretinal membrane. However, internal limiting membrane peeling is difficult in patients with retinitis pigmentosa and could cause inner retinal damage to the impaired retina.

In conclusion, we observed that implant of the Argus II epiretinal prosthesis may be complicated by the formation of a hyperreflective epiretinal band, detectable by SD-OCT. The band could have an impact on array function, as demonstrated by the increase in electrical thresholds. Large series evaluations are needed to understand the frequency of this complication, to clarify the mechanisms underlying the phenomenon, and to define evolution in time, impact on visual perception, and impact on prosthesis function. They could also clarify whether internal limiting membrane/ERM removal should be part of standard Argus II surgery.

Key words: Argus II, epiretinal fibrosis, epiretinal prosthesis, retinal prosthesis, retinitis pigmentosa.

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