Restriction of eye motility in patients with RETINA IMPLANT Alpha AMS

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ABSTRACT.
Purpose: To evaluate the motility of the eye in patients with the RETINA IMPLANT Alpha AMS.
Methods: Eye motility was determined in eight gaze directions in ten blind retinitis pigmentosa patients, who had received the RETINA IMPLANT Alpha AMS, before implantation of the subretinal implant and at six time-points up to one year after.
Results: The analysis of eye motility showed a restriction in the upgaze and gaze to the temporal side directly after surgery in eight of the nine patients included. The degree of motility restriction decreased continuously with recovery during the observation time. One year after surgery, eye motility was still restricted in the majority of patients, especially in the upgaze to the temporal side at 20° (five of seven patients).
Conclusion: Retinal implants with intraorbital parts (e.g. connecting cables) caused restriction in the temporal and superior viewing directions in the majority of patients. Although this restriction might be cosmetically visible, this limitation in eye motility has no effects on the monocular vision and the implant’s efficacy for daily use.

Key words: eye motility – orbital surgery – retinitis pigmentosa – retinal prosthesis inherited retinal degenerations

Introduction
Retinitis pigmentosa is a group of rare hereditary retinal diseases leading to degeneration of photoreceptors and causing blindness usually in middle-aged patients (Verbakel et al. 2018). Retinal degeneration is at first limited to the photoreceptors, while inner retinal neurons (bipolar and ganglion cells) remain detectable for many decades thereafter (Santos et al. 1997; Kohler et al. 2001). In the last few decades, research on the electronic restoration of vision in hereditary retinal diseases has led to two CE-approved approaches available for patients: the epiretinal implants (Argus® II (Second Sight, Sylmar, California) and IRIS® II (Pixium Vision, Paris)) and the subretinal implant (Retina Implant Alpha AMS (Retina Implant AG, Reutlingen, Germany)) (Zrenner 2012; Zrenner 2013; Stingl et al. 2017; Mills et al. 2017).

The subretinal implant Alpha AMS, shown in Fig. 1, is an active retinal implant consisting of a subretinal microchip, a retroauricular transdermal coil with a connecting cable and an external hand-held device for power supply. The subretinal microchip absorbs light that enters the eye bulb, similarly to the photoreceptors in a healthy eye (Zrenner 2002). A local current is generated and enhanced by an electronic amplifier for each electrode, to stimulate the bipolar and ganglion cells of the retina. The neuronal output uses the physiological pathway of the optic nerve to create visual perceptions in the brain. The implant is capable of absorbing light in different lighting conditions such as bright sunlight and twilight (Daschner et al. 2018). Compared to the epiretinal approach, patients can utilize microsaccades, eye movements and
head rotations as during natural vision (Zrenner 2002).

To prevent movements of the intraocular parts of the implant causing retinal damage, for example detachment or retinal tears (Gekeler et al. 2007), the connecting cable is fixed to the sclera where it exits the eye bulb (Fig. 1). As the straight intraorbital cable routing in previous models led to cable breakage, the intraorbital cable in the RETINA IMPLANT Alpha AMS forms a loop close to the eye bulb to minimize the mechanical forces of eye movements on the cable fixation points (Fig. 1). The cable finally leaves the orbit via an L-shaped canal in the bone of the lateral orbital rim (Koitschev et al. 2015). It then connects to a subperiosteal cable which ends at a ceramic housing subperiostally under the temporal muscle in the retroauricular area (Besch et al. 2008; Zrenner et al. 2011; Koitschev et al. 2015; Stingl et al. 2017). An external transducer inductively provides the necessary energy and control signals for the subretinal amplifiers. It is connected to a hand-held control unit to adjust stimulation parameters such as brightness, contrast or frequency and pulse duration of the retinal implant (Besch et al. 2008; Koitschev et al. 2015).

This paper addresses the question of whether the subretinal implant Alpha AMS with intraorbital cable routing affects eye motility in the patients.

### Methods

#### Participants

Ten participants (4 male, 6 female, mean age $\pm$ SD = 57.3 years $\pm$ 11.7, age range 34.3–70.9 years) received the RETINA IMPLANT Alpha AMS (Retina Implant AG, Reutlingen) in one eye. All patients were blind due to an end-stage hereditary retinal degeneration and were participants of the clinical trial ‘Safety and Efficacy of Subretinal Implants for Partial Restoration of Vision in Blind Patients’ (ClinicalTrials.gov NCT01024803). All participants gave written informed consent in accordance with the guidelines of the Declaration of Helsinki. The trial was approved by the local institutional review boards of the participating centres in Germany (Dresden, Kiel, Tübingen).

#### Eye motility

Eye motility was evaluated in the nine viewing directions (straight, upgaze straight, upgaze temporal, upgaze nasal, gaze to the temporal side, gaze to the nasal side, downgaze nasal, downgaze and downgaze temporal) at seven time-points (before surgery, days 1–21, month 1, month 3, month 6, month 9 and month 12). The number of patients at each visit varied. Table 1 shows the time-points of examination for each subject.

Eye motility was examined by an orthoptist and estimated in all nine gaze directions to 20°. It was evaluated qualitatively (restriction present or absent), as manifest strabismus in eye position beyond 20° from the primary position in cases does not bother patients in everyday life.

| Patient ID | Days 1–21 | Month 1 | Month 3 | Month 6 | Month 9 | Month 12 |
|------------|-----------|---------|---------|---------|---------|---------|
| DD-02      | x         | x       | x       | x       |         |         |
| DD-04      | x         | x       |         |         |         |         |
| KI-03      | x         |         |         | x       |         |         |
| KI-04      | x         | x       |         |         |         |         |
| TU-16      | x         |         | x       | x       |         |         |
| TU-18      | x         |         |         | x       |         |         |
| TU-20      | x         |         |         | x       |         |         |
| TU-21      | x         | x       | x       |         |         |         |
| TU-23      | x         | x       | x       |         |         |         |
| TU-24      | x         |         |         |         |         |         |

Subject DD-02 was excluded from postoperative eye motility testing due to eye motility restrictions prior to implantation surgery.

### Implantation/surgical procedure

The electronic subretinal implant was implanted according to the procedure as published earlier (Besch et al. 2008; Gekeler et al. 2010; Gekeler et al. 2018). First, a retroauricular opening is provided for the fixation of the power supply and control signal system housed in a ceramic box compartment in the periost (Besch et al. 2008; Koitschev et al. 2015). Secondly, a tunnel beneath the temporal muscle is generated to lead the extraorbital cable anterior to the orbital rim. Thirdly, intraocular surgery is performed (see Gekeler et al. 2010; Gekeler et al. 2018). From a temporal superior scleral flap, the tip of a polyimide foil with the active microchip is pushed in the subretinal space along a leading foil towards the fovea, resulting in a preferably subfoveal position of the microchip (Stingl et al., 2013a, Stingl et al. 2013b). The polyamide foil leads in the subretinal space in anterior temporal direction and leaves the eye penetrating choroid and sclera at the equatorial region (Fig. 1).

In a next step, the ceramic adapter plate that connects the intraorbital polyimide foil with the extraorbital silicon cable is sutured to the sclera (Gekeler et al. 2018). To provide a stable cable connection even during eye movements, the silicone cable forms a parabulbar loop beneath the eye bulb.
This technique enables the distribution of the occurring forces during eye movements on a longer cable segment and reduces the cable breakage. The surgical procedure with a parabulbar loop was the consequence of cable breaks in cases with a short intraorbital cable (Kernstock et al. 2011).

**Data analysis**

We first quantified the number of patients who showed a limitation in eye motility. Secondly, we evaluated which of the nine gaze directions was predominantly restricted. One subject (DD-02) was excluded from analysis due to eye motility restriction prior to surgery (Table 1). Due to the small sample size, we analysed the data descriptively.

**Results**

An example of the gaze restrictions encountered is shown in Fig. 2. Nine patients were included in the final analysis. In Fig. 3, the histogram depicts the number of patients with reduced ocular motility at each time-point. Eight of nine patients showed eye motility restriction at days 1–21 postsurgery, six of seven patients at month 1, six of eight patients at month 3, five of five patients at month 6, six of six patients at month 9 and four of six patients at month 12 after surgery.

The evaluation of eye motility in the nine viewing directions is shown in the radar chart in Fig. 4. It will be seen that there was no restriction in the downgaze at any of the six time-points (days 1–21, month 1, month 3, month 6, month 9 and month 12). Directly after implantation (days 1–21), seven of nine participants showed a motility restriction in the upgaze temporal and temporal gaze direction, four of nine patients had a restricted upgaze and downgaze temporal, three of nine patients had motility restrictions in the upgaze nasal, and one of nine patients had a restriction in the nasal gaze and the downgaze nasal. At the earlier time-points (days 1–21, month 1, month 3 and month 6), eye motility was predominantly restricted temporally (downgaze temporal, temporal gaze and upgaze temporal) and in the upgaze (nasal, temporal and straight). In contrast, at the later time-points (month 9 and month 12) eye motility restriction refined and occurred predominantly in the temporal upgaze. One year after surgery, five of seven participants showed a motility restriction in the upgaze temporal, three of seven patients had limitations in the nasal upgaze, two of seven patients had motility restrictions in either the temporal gaze, the downgaze temporal or the upgaze, and one of seven patients had restriction in either the nasal gaze or the downgaze nasal. The degree of motility restriction was usually mild without effect on the primary eye position and not exceeding 20° (Fig. 5).

**Discussion**

The present paper analyses the eye motility restriction in 10 patients after implantation of the subretinal implant RETINA IMPLANT Alpha AMS (Retina Implant AG, Reutlingen). Directly after surgery, eye motility was restricted, predominantly in upper and temporal viewing directions, while one year after surgery, eye motility restriction was less pronounced and mostly to the temporal upgaze direction.

Positioning the retinal implant beneath the retina is crucial (MacLaren, 2017), as the localization of the subretinal implant in the macular...
region goes along with reduced stimulation thresholds (Humayun et al. 1999) and better functional outcome (Stingl et al., 2013a; Stingl et al. 2013b). The importance of fixation has been shown in animals (Gekeler et al. 2007). Prevention of movement of the retinal implant is important in order to avoid retinal damage such as retinal tears and retinal detachment. Of note, despite cable movements during gaze changes, only minor position changes of the subretinal implant Alpha AMS occur in the majority of patients after implantation (Kuehlewein et al. 2019).

During the first days after surgery, eight of the nine patients showed eye motility restriction (Fig. 3). Postsurgical swelling can take account for this high percentage of restriction of ocular movement limitation. The surgical access to the orbit was from the temporal superior side. In the first days after surgery, the exudative phase of wound healing takes place causing swelling, tenderness or pain and haemorrhages in the wound region. Indeed, the majority of the patients showed these effects immediately after surgery, as can be observed also in the gaze direction images of one exemplary patient (Fig. 2B). As the surgical access to the orbit was from the temporal superior side as well as most intraoperative manipulation, swelling occurred predominantly in this region with limited eye motility.

Up to 3 months after surgery, until the wound healing process is terminated, cicatrization is possible in the area of surgery inside the eye socket. This is the typical time-point for the final examination after strabismus surgery to evaluate the surgical results (Kaufmann & Steffen 2012). Until then, suturing material in the orbit is integrated by ingrowing connective tissue (Rohrbach et al. 1997) and the remodelling phase of wound healing is finished (the type III collagen fibrils are replaced by the more robust type I collagen fibrils) and a heavy-duty scar exists (Seebauer et al. 2019).

There are several reasons for the remaining restriction of eye movement three months after surgery. First, a too short cable length within the orbit, connecting the exit from the eye bulb with the exit of the orbit, could be responsible for the reduction in eye motility. To ensure free eye movement at the downgaze, which is crucial for

![Fig. 3](image1.png)

**Fig. 3.** Numbers of patients with reduced ocular motility after implantation of the RETINA IMPLANT Alpha AMS. Bar diagram displaying the number of patients with eye motility restriction after implantation of RETINA IMPLANT Alpha AMS. The x-axis displays the time postsurgery up to 1 year. Black bars indicate the absolute number of patients tested at the particular time-point, while dotted bars represent the absolute number of patients with eye motility restriction.

![Fig. 4](image2.png)

**Fig. 4.** Direction of eye motility restriction. The radar chart displays the percentage of patients with eye motility restriction after implantation of the RETINA IMPLANT Alpha AMS in eight viewing directions (upgaze straight, upgaze temporal, upgaze nasal, temporal gaze, nasal gaze, downgaze nasal, downgaze and downgaze temporal) at six time-points (days 1–21, month 1, month 3, month 6, month 9 and month 12) (colour-coded). Eye motility was predominantly restricted in the temporal upgaze, while no limitations were observed in the downgaze.
grazing the temporal superior orbit at the scleral flap (Gekeler et al. 2018). This scarring could additionally lead to the observed eye motility restriction in the analysed data set.

Unilateral eye motility restriction, for example after trauma, normally results in double vision if binocular seeing is possible (Wagner 2012). However, the RETINA IMPLANT Alpha AMS was implanted only in one eye during the clinical trial; thus, none of the patients had binocular vision due to the end-stage of retinal degeneration of the other eye. Thus, the restricted eye motility by the RETINA IMPLANT Alpha AMS does not limit its suitability for daily use. Although the efficacy results varied substantially among the patients (Stingl et al. 2017), functional vision in the straight gaze was not limited by the temporal restrictions in any of the patients.

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