Case Report

Highest reported visual acuity after electronic retinal implantation

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ABSTRACT.

Purpose: To report the highest attained visual acuity with an electronic retinal implant for the treatment of advanced retinal degeneration following a novel intensive period of visual training.

Methods: A case study as part of the prospective, international, multi-centre, interventional clinical trial (ClinicalTrials.gov NCT02720640 and NCT01024803) of patients with the Retina Implant Alpha AMS (Retina Implant AG, Reutlingen, Germany) for advanced retinal degeneration. A patient with subretinal device implanted into worse-seeing eye with no useful perception of light vision secondary to USH2A retinal degeneration underwent intensive period of visual training.

Results: The device remains functional with no safety concerns at 3 years postsurgical implantation, and following visual training, the patient achieved the highest visual acuity so far with an electronic retinal device, with real, digitally unenhanced, reading vision of 0.04 decimal (equivalent to 1.39 LogMAR and 20/500 or 6/150 Snellen). In addition, perception as well as partial identification of obstacles and evaluation of distances was possible in both daylight and nighttime settings.

Conclusions: Retinal implants are currently the only available therapy option for advanced retinal degeneration. Visual rehabilitation postimplantation has potential to maximize visual percepts. The novel concept of intensive visual training presented herein shows what is achievable with electronic retinal implants and has implications for other therapeutic options, such as optogenetics, that aim to stimulate remaining inner retinal cells in advanced retinal degeneration.

Key words: electronic prosthesis – inherited retinal degeneration – retinal implant – visual rehabilitation

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Introduction

Inherited retinal degenerations are the leading cause of blindness in the working-age population (Liew et al., 2014) with the global prevalence of 1 in 4000. Over the last two decades, novel approaches have emerged for the treatment of affected individuals and are broadly divided into those suitable for early stages of degeneration where photoreceptor rescue is possible (gene replacement therapy) and those that are more applicable in advanced stages where majority of the photoreceptors are lost (electronic retinal implants, optogenetics and cell therapies).
Electronic retinal implants are currently the only approved therapy option for advanced-stage inherited retinal degeneration.

In addition to the first-generation Retina Implant Alpha IMS, which gained CE Mark in 2013, there are three main bionic eye systems for the treatment of inherited retinal degenerations: Retina Implant Alpha AMS, Argus II and IRIS II with their key differences summarized in Table S1. In essence, the Alpha systems use a photodiode array implanted in the subretinal space proximal to the highest order surviving cells after photoreceptor degeneration (e.g. horizontal, bipolar and amacrine cells) with potential to maximize natural retinal visual processing. In addition, the photodiodes allow for the detection of light as well as charge transfer to the retina, obviating the need for external devices for light detection (Daschner et al. 2018). The epiretinal devices, Argus II and IRIS II, adjoin the retinal ganglion cell layer and deliver electrical impulses to the retina following external light detection through a video camera and a processing unit.

The safety and efficacy data have been published for the Alpha devices (Stingl et al. 2015; Stingl et al. 2017; Gekeler et al. 2018; Edwards et al. 2018) and for the Argus II prosthesis (Humayun et al. 2012; da Cruz et al. 2016) with comparable results reporting functional benefit in patients with profound visual loss. The best reported visual acuity of 20/546 (6/164) was reached by two patients on Landolt-C ring testing with Alpha devices at 12 months postimplantation (Stingl et al. 2015; Stingl et al. 2017). The maximum visual acuity with the Argus II system was 20/1262 (6/379) when tested with gratings at 12 months postsurgery (Humayun et al. 2012). Herein, we describe a case of an Alpha AMS device user who attained the highest retinal implant-mediated visual acuity of 20/500 (6/150) at 3 years postimplantation following a novel visual rehabilitation regime.

Methods

A 45-year-old female subject (OX-RI-01) was recruited at Oxford Eye Hospital as part of the international, multi-centre, interventional clinical trial (ClinicalTrials.gov NCT02720640 and NCT01024803) of patients with the Retina Implant Alpha AMS (Retina Implant AG, Reutlingen, Germany) for advanced retinal degeneration. The research is in accordance with the guidelines of the Declaration of Helsinki (seventh revision, 2013) and has National Research Ethics Committee approval (ref. 15/LO/0445). The trial eligibility criteria, the surgical procedure and clinical end-points have been previously described (Edwards et al. 2018).

In addition to the functional assessments undergone by the subject as part of the trial, the patient was recruited to an intensive visual rehabilitation programme, 3 years after insertion of the retinal implant. The programme took place in a specialist centre in Reutlingen, Germany, as part of the novel visual rehabilitation scheme in patients with retinal implants. The details of the 5-day intensive training programme are outlined in Table S2. The focus of the rehabilitation was on subject’s reading ability and outdoor orientation. During all sessions, glasses were worn with refractive correction and occlusion of the non-operated eye. The subject was trained every day for 2 h in front of a light box and a screen reader placed at 55 cm during which she practiced various shapes and letters with different fonts and sizes. Short words such as YES, YOU, LOVE, MOTHER and CAKE were presented each day, with at least 3 spaces between the letters. The task was repeated several times during the 2-h training/assessment period, with no time limit on each trial. The visual acuity was estimated from the reading vision, based on the size of the letters and shapes presented, similar to recognition tasks used in formal clinical trial settings (Stingl et al. 2015, da Cruz et al. 2016 and Edwards et al. 2018). Further spatial resolution testing, such as basic grating acuity or Landolt-C ring optotype, that was performed during the initial clinical trial period (Stingl et al. 2015, da Cruz et al. 2016 and Edwards et al. 2018) was not repeated during this rehabilitation programme, which was not set up to replicate the formal clinical trial

Fig. 1. Retinal images (Heidelberg Engineering Inc., Heidelberg, Germany) of the Alpha AMS implant (Retina Implant AG, Reutlingen, Germany): (A) A wide-field image (A), an autofluorescence image, with incidental optic nerve head drusen (B) and an optical coherence tomography scan (C) demonstrating a well-positioned subretinal chip fully in contact with the overlying neurosensory retina 3.5 years postimplantation
conditions. Visual acuity however is defined as the minimal angle of resolution of two points, and so this stands whatever format the points are in.

In addition to the letter recognition task, recognition of simple and complex shapes in different sizes was trained and tested on daily basis during the programme. The tasks were performed under different contrast settings and magnification levels, until the preferred setting was determined, as specified in Table S2. The programme also trained hand-eye co-ordination using the tabletop objects. Lastly, the rehabilitation heavily focused on indoor orientation following an artificial path and on recognition of obstacles and estimation of distances in outdoor conditions (Table S2).

Results

A successful retinal implantation surgery was performed in a 45-year-old patient at the Oxford Eye Hospital, UK. The patient had advanced retinal degeneration secondary to two genetically confirmed mutations in USHA2A (c.2276G>T and c.11549-1G>A). The implant was placed subretinally into the patient’s worse-seeing eye with no useful perception of light vision and a reliable electrically evoked phosphene response. At 3 years postimplantation, the chip remains well positioned in the subretinal plane at the macula, maintaining complete uninterrupted contact with the residual inner retina (Fig. 1). Except for conjunctival erosion over the foil at 2 months postsurgery (successfully repaired at the time), there were no additional adverse events or safety concerns.

At the study visit at Reutlingen, Germany, at 3 years postimplantation, the patient reported overall subjective satisfaction with the implant. She found the implant (switched ON and not OFF) useful in certain aspects of her daily life and especially during her daily walk to the local pool in order to avoid obstacles. Following intensive visual rehabilitation programme (Fig. 2 and Table S2), OX-RI-01 achieved the best reading vision so far (implant ON) using a screen reader at 55cm to identify different letters and read short words (e.g. LOVE, CAKE) presented with different fonts (e.g. Ariel 10, magnification 9, letter height 3.5 cm) (Fig. 2A). On the fourth day of training, all letters within short words were identified, although sometimes in an incorrect order, for example LOVE would be read as O. L. V. E. The visual acuity was estimated from the reading vision with patient passing spatial resolution of 0.04 decimal, equivalent of 20/500 (6/150) Snellen fraction or 1.39 LogMAR (Table 1). The visual assessment was real and did not involve digitally enhanced images from a camera.

In addition, simple and complex shapes in different sizes were trained including circles, triangles, arrows and various symbols (Fig. 2B). Recognition of small shapes was consistently achieved in strong contrast settings. At the light box, patient was able to identify the symbol of a woman and man (as used on restrooms) including gaps between legs as well as body and head with estimated visual acuity of 0.0048 decimal (6/1250 Snellen; 2.2 LogMAR). Having practised hand-eye co-ordination at the table the day before, when presented with a set of 3-
Table 1. Visual assessment performance achieved by Retina Implant OX-R1-01 user after extended intensive training

| Training objective                                | Achievement                                                                                                                                 |
|--------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Recognition of shapes, letters and numbers       | Yes (‘O’ and ‘L’ usually first to be identified even with 4 –6 letters on screen). Estimated highest visual acuity of 0.04 decimal (6/150 or 20/500 Snellen; 1.39 LogMAR). |
| Reading of short words                           | Yes (order of letters sometimes incorrect and high contrast and magnification preferred). Estimated highest visual acuity of 0.04 decimal (6/150 or 20/500 Snellen; 1.39 LogMAR). |
| Recognition of novel/complex shapes              | Yes. Excellent small shapes identification with good contrast. Many complex shapes identified, for example symbol of a man/woman as used on restrooms in public places (estimated visual acuity of 0.0048 decimal (6/1250 Snellen; 2.2 LogMAR). |
| Hand-eye co-ordination                           | Yes (required correction by 3-4 cm). Yes (without any difficulties). Daylight: Yes (e.g. identification of yellow post box as an obstacle). Nighttime: Yes. Different street lights, car headlights and the brightly lit shopping windows were perceived but identification was difficult. |
| Following artificial path                        | Daylight: Correct identification of arches v rectangular windows in an old monastery with correct estimation of distances. Path of gravel in the meadow followed without assistance. | |
| Recognition of obstacles and estimating distances|                                                                                                                                             |

Digital shapes, patient was able to sort the objects in pairs (2 triangles, 2 squares, 2 circles) and recognize an arrowhead with the correct orientation. Hand-eye co-ordination had to be corrected by about 3–4 cm.

The training programme also heavily focused on orientation and visual perceptions and interpretations in indoor (Fig. 2C) and outdoor settings (Fig. 2D). The subject was able to follow a laid out artificial path in good contrast (Fig. 2C and Table 2 in the Supplement). Outdoor orientation (Fig. 2D) involved two walks in two small towns with old structures, one during daylight and one at night. After training, the patient was able to locate objects in surroundings (e.g. a yellow post box was found as obstacle), recognize and track lines for orientation (a gravel path was followed in the meadow without assistance) and correctly estimate distances (Table 1).

Discussion

Alpha AMS implant-mediated visual perception attained in this case of profound visual loss secondary to retinal degeneration is the highest reported visual acuity recorded with an electronic retinal implant, so far. This visual performance was achieved at 3 years postimplantation following a novel rehabilitation programme with additional improvements in patient’s reading ability and orientation outside. The superior durability of the implant compared to the previous generation Alpha IMS model is critical in this sustained process.

The interim results for patients with subretinal Alpha AMS implants showed encouraging functional benefits (Stingl et al. 2017; Gekeler et al. 2018; Edwards et al. 2018). In particular, for the patient described herein, visual gains were reported in activities of daily living and basic vision assessments, with the best performance achieved on detecting grating orientation with a spatial frequency of 3.33 cpd (1.26 LogMAR; 0.055 decimal; 6/109 (20/364) Snellen equivalent), albeit only on one occasion (at 6 months) that was not reliably repeated on Landolt C-ring testing (score of <75% in 2-alternatives forced-choice tests; Edwards et al. 2018) suggesting a disparity between the 2 methods of acuity determination.

For very low vision, reliable optotype recognition ability is challenging and cannot directly be compared with grating acuity because the detection of grating lines involves stimulation of multiple and dispersed photosensor areas, that are perceived as long lines.

Despite the continued user-reported benefit from the implant following the initial 12 months of study prescribed follow-up, especially during outdoor activities, the subject’s overall motivation had declined and she found that the use of implant was slowing her down on occasions and especially when used in familiar environments. This prompted a top-up rehabilitation on practical use of the implant. This special training session was scheduled to test new tools and an intensive training concept, with short sessions every day. The focus was on reading ability and orientation. The late-phase rehabilitation resulted in unexpected re-learning of vision at highest levels reported so far (1.39 LogMAR and 20/500 or 6/150 Snellen). The patient’s reading ability of small letter words improved with training, and she was able to read the words correctly on several occasions, consistently passing the estimated visual acuity of 0.04 decimal or 1.39 LogMAR. In addition, detection and localization of high contrast objects was achieved, although recognition in the sense of shape perception and interpretation remains more difficult. After the training, the patient achieved excellent recognition of small shapes in high contrast. Moreover, identification of some complex shapes was possible, that might be useful in improving mobility and orientation. The implant user seemed eager to go on, now that she had seen what was possible with some training effort. It is likely that this active participation and patient’s ability to manipulate the screen reader herself stimulated learning and had overall positive effect on the patient.

This unexpected gain in visual function could be due to rehabilitation and re-learning of vision, but could also relate to improvement in retinal function with reduced retinal oedema and/or better embedding of the chip electrodes in the retina over time. Nonetheless, the gain is still below the maximum theoretical spatial resolution of an electronic retinal implant. For the Alpha AMS system, this is estimated to be 1.1 LogMAR or
20/280 (6/84) Snellen based on two-point discrimination (Table S3). The theoretical maximum acuity might have been achieved with a more subfoveal chip placement. During the reading task, the patient reported several separate perceptions of light at once when looking at several small letters on the screen, indicating a wide visual field, good retinotopy as well as general excitability of the retinal layers. This suggests that young patients with rod–cone dystrophies, such as USH2A related dystrophy, with recent loss of residual cone vision and before significant remodelling has taken place, may represent ideal candidates for retinal implants. Thus, careful phenotyping and patient selection may improve future outcomes in patients undergoing retinal prosthesis or alternative therapies such as optogenetics (Cehajic-Kapetanovic et al. 2015). In addition, as well as early postoperative rehabilitation the continuous motivation and long-term periodic intensive training sessions with specialized teams are necessary to maximize the implant-activated visual percepts.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Currently approved retinal prostheses for patients with inherited retinal degenerations.

Table S2. Details of the intensive training programme undergone by a Retina Implant Alpha AMS user in a specialist centre in Reutlingen, Germany.

Table S3. Theoretical spatial resolution achievable with the Retina Implant Alpha AMS system. Calculation is based on a reduced eye model.
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