European Aniridia Conference | 31.05.- 02.06. STOCKHOLM 2024

June 2nd, 2024
European Aniridia Conference, Stockholm

Popular Summary for Patients by Prof Neil Lagali

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The conference started with our Keynote speaker Tor Paaske Utheim, who spoke about dry eye disease: mythis and facts, the take-home message is the importance of breaking the vicious circle of dry eye disease, the sooner the better, and remember that dry disease is an inflammatory disease. This is something we should not forget, because we know that in aniridia, dry eye disease is very prevalent. We also know that there is Meibomian gland dysfunction in aniridia. Even if the tear production is normal, the Meibomian glands are dysfunctional. We also know that PAX6 affects the development of the lacrymal gland as well. And the whole tear film and its composition is affected in aniridia. The tear film is so important in maintaining the health of the ocular surface.

We now move on from the keynote speaker to the session on glaucoma. Here, Peter Netland has been very kind to provide his insights. Here the message is that glaucoma drainage devices have been used widely in aniridia and they function well, they are a good means to reduce the interocular pressure. But it is a surgery and all surgeries are invasive and surgeries carry risks as well. And this has to be kept in mind for both patients and for the doctors. But there are some very interesting new technologies, such as minimally invasive glaucoma surgeries that are starting to be done more so in the United States. Now these are also coming to Europe, and are really very promising surgeries for control of glaucoma in the future. We are hoping that this type of surgery, like the Xen stent implant, is going to be able to be translated specifically to aniridia because this can be a very quick surgery that can really

improve the drainage and has fewer side effects than the traditional glaucoma surgery. In the coming years we hope that more clinical evidence is going to be built up in this area.

We then had a very important session on new research areas in aniridia looking at effects outside of the eye. Looking at quality of life in aniridia, there are multiple ways of gathering information. We had designed new questionnaires, but also the importance of stories, interviews and narrative medicine in documenting the lived experience of patients and families with aniridia is so important. We have seen here during the conference that the patient and caregivers' experiences have to be taken into account when thinking about treatment, when thinking about how are we going to improve the quality of life of patients with aniridia, and I think we are starting to realize this more. These types of studies and types of outcome measures are very important, and we are recognizing this now on the research side as well. Part of the purpose of this conference is to get the message about quality of life and lived experiences of those with aniridia across to the medical profession. This whole discussion was very interesting.

James Lauderdale presented some very important research on aniridia and its effects in the brain. The message was that there are documented effects of aniridia in the brain, different parts of the brain that affect different systems and can to a large degree explain a lot of the symptoms that we know that people with aniridia experience. From the sense of smell, sense of taste, the hearing, the auditory processing, as well as the pineal gland, for example, with production of melatonin, sleep disturbances, and eating disturbances that many of you are very familiar with, and the neurological and endocrinological effects as well. All of these can be traced back to PAX6 and its key roles in various systems and in the brain during development. This includes the pancreas. We also heard about and the risk for developing diabetes because of impaired glucose and insulin regulation in the body in aniridia. This is also a very important aspect of the health-related quality of life in congenital aniridia.

We next had a session on artificial iris, cataract and the posterior segment. Vito Romano summed up the state of our knowledge in a systematic review of artificial iris implantation with the existing devices that we have today. The artificial iris is in almost 100% of cases implanted at the same time as the cataract surgery. This is good, of course, to minimize the number of surgeries. But it has been shown based on all the literature that we have, that the artificial iris devices have a significant risk for worsening the glaucoma that's already present in these eyes as well as stimulating new glaucoma in patients who didn't have glaucoma initially. These are important considerations. Even if the literature is showing that the visual acuity is improved with the surgery, it's impossible to separate if that visual acuity improvement was due to the cataract surgery or was it due to the artificial iris? Most of the vision improvement is likely because of the cataract surgery.

It is not clear if there is really any benefit of an artificial iris in terms of the vision. We have also heard at the conference from the small Belgian company Azalea Vision that the smart scleral contact lens they are developing and the pinhole effect of the iris within that lens can help with vision, as well as photophobia.

This was followed by a presentation by Dominique Bremond-Gignac, about posterior segment anomalies in PAX6-related congenital aniridia. One of the main points was the foveal hypoplasia that can be graded and how this relates to the presentation of the iris hypoplasia, that is not always easy to see. One of the examples given was that a patient with aniridia could have almost a full iris but have a complete foveal hypoplasia.

If you can examine the fovea from childhood or even in infants, it can provide important information about the potential for visual rehabilitation. Because even if the rest of the ocular media is clear, vision is going to be limited by the foveal hypoplasia and the optic nerve hypoplasia as well.

We next had a session on keratopathy and aniridia. There were some very important cases presented about the keratopathy as well as results from register studies in Sweden and in the United

Kingdom. Cases were presented where aniridia patients have received a cornea transplant. The key message was that we do not see good outcomes for cornea transplantation. Cornea transplantation fails in aniridia, and this is because of many reasons, including being a foreign tissue being placed in the eye. There is an immune load on the eye, and there's already an immune compromised status in the eyes of people with aniridia. This makes transplantation a high risk procedure, meaning that the chance for success is already quite low. We also discussed about how to define success. Medical success for the surgery is not the same as a successful outcome for the patient. What we see with the transplantations is that you can get a temporary clarity of the cornea after the procedure, so vision can slightly improve, but it's limited in time, and eventually the keratopathy will come back. A patient might get one to two years of vision improvement, and even in some rare cases, maybe three years of vision improvement. But the keratopathy is going to come back again and not only that, but after the procedure patients need to be immunosuppressed, systemic immunosuppression and local immunosuppression in the eye - this can be quite a burden for patients.

This means that both patients and families, and of course, the doctors need to seriously have a good discussion about this and consider the risks involved versus the potential gain or benefit. We saw some information about stem cell transplantation and corneal transplantation together, which can work in eyes that are not aniridia eyes. But when you consider an aniridia eye, there is a much higher risk for transplant failure.

So this has to be considered. Just because a stem cell therapy is available, it doesn't necessarily mean that is a good option for aniridia, although we do keep our hopes for stem cell therapies in the future. This leads us to our session on stem cells in aniridia. There were different insights based on analyzing patient material, patient tissues from those who have undergone surgery, but also cells derived from material donated by patients with aniridia, and programming those cells to become stem cells and what we can learn from that. We can think about this as potentially being a path to a future treatment. But we're not there just yet. It's going to take

years before we can see some of these new stem cell technologies potentially being applied to the eye in aniridia. But we are learning a lot from this research right now, and that can be of great benefit for aniridia in the future.

One of the messages is that all is not lost, that there is evidence that there are stem cells still in the corneas and the limbus of eyes with aniridia. But it's just that we have to try to figure out how to activate those. What exactly went wrong? They are not functioning as they should. It is a sign of hope that we do at least see these this evidence of stem cells that are still present in aniridia. It is for the researchers to try to figure out what are the mechanisms, what's happening, and how can we try to promote those stem cells to do what they're supposed to do so that we prevent the vessels growing into the eye. The vessels in the cornea that impact the vision so much. There is a lot of research going on in this area, so there is reason for hope.

We next had a session on genetics and aniridia, where Maria Moosajee and Sophie Valleix presented. One of the take home messages was that it is very important to have genetic analysis where we can in aniridia, although it is not available everywhere in every country. But where it is possible, it is strongly recommended to have the genetic report because even today, that can tell us something about what effects aniridia will have in the eye. What is the prognosis? Will a child maybe have systemic effects or not? It can also help, also in the context of genetic counseling as well, to know what the actual affected gene and mutation is. It is also important for the future, because the more and more we learn about the genetics, the more and more important it is going to be to really have well-documented genetics for the patient.

Also, in our way of talking about aniridia in the medical profession and as researchers, because the disease is so diverse, we need to start using the genetics in guiding us how to describe what a patient actually has. This is about what kind of mutation but also what kind of phenotype they have. We shouldn't underestimate the impact of naming something and how much that can help move the medical care and the field of research forward. It is also important

to keep in mind that we are going to continue the discussions with many of the researchers here at this conference, to try to develop a consensus on how we can name this PAX-6 aniridia syndrome/spectrum. That is going to continue after this conference and that is one good thing that has come out of this conference, to try to achieve consensus on naming the disease and its variants.

We then had a session on management of aniridia, especially in children. We heard from Fabian Fries and Nora Szentmary from the Schwiete Center for Aniridia in Homberg where a lot of patients with aniridia in Germany are being treated. From the hundreds of patients there, we learned what the data is telling us about the progression of the disease and how this is being managed. Dominique Bremond-Gignac then presented in the session about the guidelines for aniridia. The guidelines are so important for many different groups, for the patients and for doctors. We have guidelines in several specific countries, but we don't have a pan-European guideline. This is something that's going to happen very soon and the European guidelines can be spread to many different groups and countries to serve as a resource. That is really going to help with aniridia care and be a resource for patients as well.

This is a work in progress, but it's going to happen soon, with a lot of people here at the meeting being involved with that, and Dominique spearheading these efforts based on the French aniridia guidelines and the COST Action working group.

This morning, we had a session on gene therapy approaches including a talk by Elisabeth Simpson, showing us new mouse models of aniridia and how important those are and how important it is that they mimic what's really happening in the in patients with aniridia. And we're getting closer and closer to having an excellent model of the human disease, which is really promising because the better model we have for the human disease, the more things we can test, and the more relevance it will have when we can develop new therapies and try to get them into first clinical trials.

I think we are already at a point where we have models that are really very good and we are using those models now. This morning

you heard two talks about characterizing these mouse models of aniridia and how close they are to what we see in patients. This is very promising.

Then we heard about some technology development. Andrew Hopkinson talked to us about the Omnigen product, which is the amniotic membrane. It is exciting that this is a non-surgical approach to using the amniotic membrane, and it is our hope that the product will make this healing tissue available to more people and to more indications than has traditionally been done to date. Andrew showed some nice results with patients with aniridia who have received this amniotic membrane and that it really did promote healing in patients. That is really something that we want to build on in the future because it would just increase the access and increase the availability of this treatment option for aniridia.

We then heard from Andres Vasques Quintero about the dynamic contact lens with customized iris built in. This is very promising, but it's going to be probably three to five years before we get a product that's available. But the company is already talking to groups with aniridia to make the device specifically for aniridia. He showed that just controlling the iris and the diameter to regulate and the amount of light in the eye can improve vision. Keeping in mind that, yes, we have the foveal hypoplasia. But I think if we can just get a slight improvement in vision, it could mean a big difference for patients functionally as well. The fact that this device does not need to have a central pupil, but it can be customized to the specific person and even to the curvature of the specific cornea, makes it a customized solution for each individual patient.

Finally, we had a good panel discussion about bringing therapies from animal models to the clinic. We see that maybe it will take three to five years if it's a drug that we're repurposing or an already approved drug, but maybe close to ten years or more if it's going to be a new therapy, a new medicine or a new stem cell therapy, for example. But it's important to keep all those lines of investigation going because of the future. We never know what's going to happen and which therapies will be the most beneficial for patients in the future.