Atropine to prevent myopia progression

Risk factors and possible treament regimens for **myopia in children**

POZNAN The prevalence of myopia in children is on the rise. Clinical studies suggest that atropine in low concentrations over a period of about two years could slow the progression of myopia.

The prevalence of myopia in children ranges from 0.7% in Saudi Arabia (children aged three to ten years) 1.4% in South America (children aged five to 15 years) to 65.5% in Beijing (age 14 to 15 years). The highest prevalence of myopia in schoolchildren was reported in East Asia and Singapore, urban areas of China, Taiwan and South Korea (Figure 1). In Europe the prevalence rates reached 42.7% in a ten- to 19-year French cohort. Non-cycloplegic measurements reported even much higher prevalence rates. For example, in South Korean children aged twelve to 18 years a prevalence of 73% was found. It is well-documented that the prevalence of myopia has increased in the last years in many parts of the world. Although the majority of available epidemiological studies come from a few Asian countries, a few North-American and European studies also confirm this trend with, however, much less magnitude.

What are the myopia risk factors?

Two major environmental risk factors for myopia onset and progression confirmed in Asian, Australian, North American and European studies are near work, especially in young age, and lack of enough outdoor activity (Table 1). Interestingly, as it was shown for example in the SAVES study, near work was a risk factor for myopia but only for the six-year-old children, and not in a twelve-year-old cohort. This suggests that near work can be an especially potent myopia inducing factor in smaller children. Moreover, it was recently shown that shorter reading distance, especially less than 25–30 cm, is a risk factor for myopia progression. The second risk factor, outdoor time, has been proven to be the strongest environmental factor that can delay myopia onset, and probably limits the progression of myopia. The most accepted underlying mechanism of time spent outdoors is based on the release of retinal dopamine that controls scleral growing and remodeling.

Children with early onset myopia will have higher duration of the disease, higher myopia progression and will be at risk of developing high myopia plus myopic macular degeneration. Thus, age of myopia onset or duration of myopia progression is the most significant prognosticator of high myopia in later childhood.

Why is the rise of myopia a problem?

It is estimated that 1.4 billion people were myopic in 2000, and it has been predicted that by 2050 the number will reach 4.8 billion. Socioeconomically, refractive errors, particularly if uncorrected, can affect school performance, limit employability and impair quality of life. But the real problem is high myopia (Figure 2) that is known to be associated with an increased risk of several ocular complications such as retinal detachment, glaucoma, cataract, optic disk changes and maculopathy. High prevalence rates of myopia is associated with increased prevalence of high myopia, in some populations 5–10% of all myopia, and this poses a major public health challenge due to the prognosis of visual impairment.

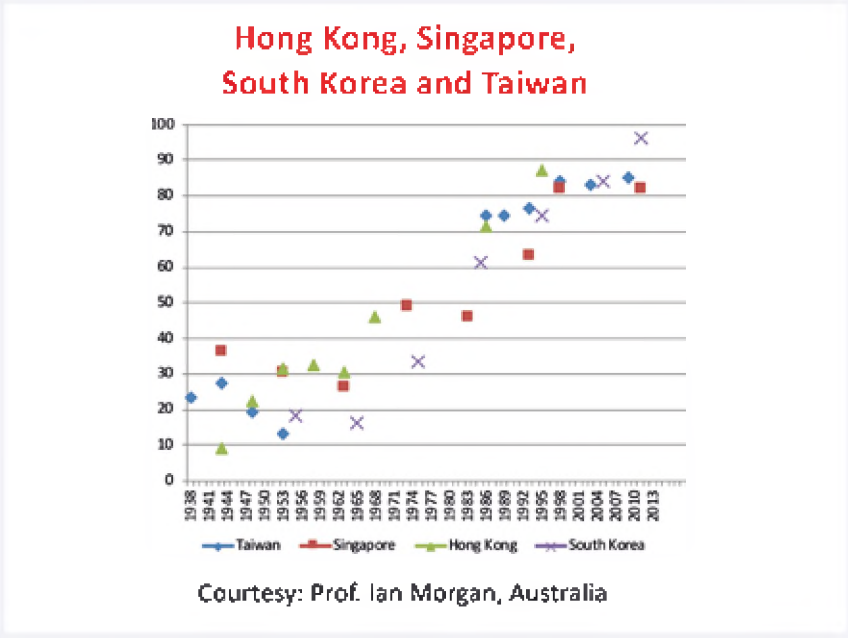

Figure 1: Prevalence of myopia in 18–20 year-olds in East and Southeast Asia. Courtesy: Prof. Ian Morgan, Australia.

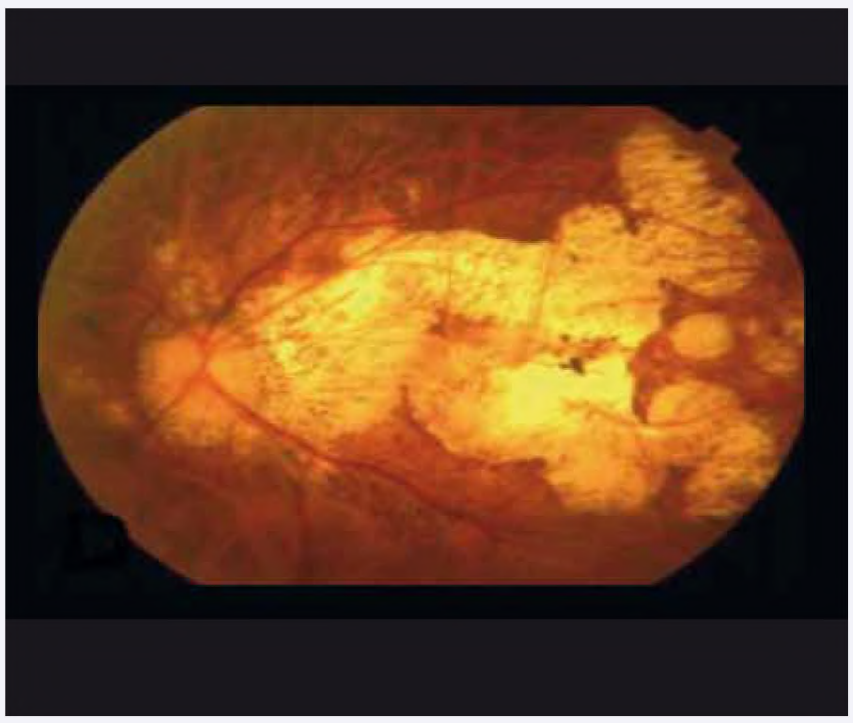

Figure 2: High myopia.

- parental myopia	- parental education
- ethnicity	- family income
- excessive use of near electronic devices (device screen time, DST)	- high pressure educational systems
- low light levels	- reading from close distance
- low time outdoors	- urban environment
- education	- female

Table 1: Myopia risk factors.

Adverse events	Atropine dose 0.01% (n=84)*	0.1% (n=155)*	0.5 % (n=161)*	1% (n= 200)**
Allergic conjunctivitis	0 (0%)	6 (4%)	7 (4%)	9 (4.5%)
Allergy-related dermatitis of the eyelids	0 (0%)	1 (1%)	3 (2%)	
Irritation	1 (1%)		2 (1%)	
Blur	1 (1%)			2 (1%)
Glare			1 (0.6%)	3 (1.5%)
Loss of distant BCVA > 1 line	11 (13%)	20 (13%)	13 (8%)	
Accomodation amplitude (D)	11.3 diopters	3.8 diopters	2.2 diopters	
Mesopic pupil size increase (mm)	1.3 mm	3.3 mm	3.8 mm	
Photopic pupil size increase (mm)	1.1 mm	2.8 mm	3.3 mm	

* ATOM 2
** ATOM 1

Source: Grzybowski A. et al. The Role of Atropine Eye Drops in Myopia Control. Curr Pharm Des. 2015;21(32):4718-30.

Table 2: Adverse events in ATOM studies.

Benefits and limitations of atropine in myopia

It is well evidenced that both pharmacological (atropine) and optical measures (orthokeratology and peripheral defocus contact lenses) are effective in myopia control in children. They differ, however, in the terms of effectiveness, safety, availability and costs. The use of orthokeratology and soft contact lenses, although they showed moderate effects for myopia control in several studies, is still limited by their invasiveness and cost. On the other hand, high-dose atropine was proved to be superior to other interventions. Atropine was used in the treatment of myopia from the middle of the 19th century on, but the first prospective, randomized and controlled trial, which confirmed its effectiveness in both spherical equivalent (SE) and axial length (AL) against a placebo group, was the ATOM 1 (Atropine in the Treatment Of Myopia, 1999–2004) study conducted in Singapore. The study included 400 children, who received 1% atropine drops or placebo daily over two years. In this study, myopia progression was reduced 77% with 1% atropine. However, major side-effects of 1% atropine, including photophobia and loss of accommodation, limit its long-term application.

This provoked some later studies comparing efficiency and visual side

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effects of lower doses of atropine: 0.05%, 0.1%, 0.25% and 0.5%. In another single-center, double-masked, randomized study (ATOM 2), the safety and efficacy of 0.5%, 0.1% and 0.01% atropine solutions during two years were studied in Singapore. Mean myopia progression and increase in AL were greater in the 0.01% group, but the differences in myopia progression and AL change between groups were clinically insignificant. Atropine 0.01% had minimal effects on accommodation and pupil size, and no effect on visual acuity (Table 2). In conclusion, atropine 0.01% had minimal side effects and similar efficacy in controlling myopia progression when compared with other dilutions.

In a five year follow up of the ATOM 2 study, authors showed that 0.01% atropine slowed myopia progression by 50%. Based on their experiences they proposed that a daily dose of atropine 0.01% is an effective first-line treatment in children aged six to twelve years with documented myopic progression of -0.5 D in the preceding year with few side effects. Moreover, because atropine appeared more effective in the second year than the first, treatment initially should be continued for at least two years.

What is better: 0.01 or 0.05% atropine?

Although there is compelling evidence that 0.01% atropine is effective and safe in five year follow up, it does not mean that other low concentrations of atropine might not be as safe and even more effective. Very interesting new data is brought by a group of researchers from Hong Kong who published in 2019 the results of the Low-Concentration Atropine for Myopia Progression (LAMP) study: a randomized, double-blinded, placebo-controlled trial of 0.05%, 0.025%, and 0.01% atropine eye drops in myopia control. Since it is the first part of a few consecutive studies it can be named LAMP 1. The authors showed that all low concentrations of atropine reduced myopia progression along a concentration-dependent response. All concentrations were well tolerated without an adverse effect on vision-related quality of life. They concluded that of the three concentrations used, 0.05% atropine was most effective in controlling SE progression and AL elon-

gation by up to nearly 70 % over a period of one year. The very interesting finding was that 0.05 % atropine was few times more effective than 0.01 % atropine. SE progression in the 0.05 % atropine was -67 % vs. -27 % in the 0.01 % atropine group; axial elongation: -51 % vs. 12 % consequently. Regarding side effects, photophobia was found in 7.8 % in the 0.05 % group vs. 2.1 % in the 0.01 % group; progressive glasses were needed in 0.9 % in the 0.05 % group vs. 1.8 % in the 0.01 % group. In the LAMP 2 study researchers will present data after two years follow up.

Since our experiences with myopia treatment are quite limited and many questions are still unanswered we created a European network for myopia control to support treatment of myopia in Europe. Everybody interested to join please send an email to: ae.grzybowski@gmail.com.

Conclusions

Although the area of unknown in myopia pathogenesis and treatment is still broad, based on present evidence we know that:

1. The prevalence of myopia increases in Asia, North American and Europe with a different dynamic that is accompanied by the rise of high myopia.
2. High myopia is known to be a risk factor for many eye diseases and is related in many cases with vision deterioration and vision loss.
3. Although genetic risk factors still might have some role in myopia pathogenesis, environmental risk factors, including near work and outdoor time, seems to have major role in the recent myopia boom.
4. It seems to be reasonable to limit unnecessary time spent on near distance activities by pre-school children, including electronic devices, and increase the outdoor activities to min. two hours per day.
5. For high-risk and quickly progressing children some optical and pharmacological strategies are available, among which low concentration atropine (0.01 or 0.05 %) provides the best risk-benefit ratio, with no clinically significant visual side effects balanced against a reasonable and clinically significant 50 % reduction in myopia progression. ■

EURETINA Session: Myopia Update 2019 – Pathogenesis, Diagnosis and Treatment
Saturday, 7.9.2019 **16.30 – 18.00**
Grand Amphitheatre

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Machine learning with inbuilt annotations

Taking **clinical support** to a new level

BERN A new custom convolutional neural network could assist in the fast and easy detection of different ophthalmologic pathologies like age related macular degeneration from optical coherence tomography scans. Importantly, the artificial intelligence system can yield capabilities that rival that of expert ophthalmologists for well defined tasks.

Optical Coherence Tomography (OCT) scans play an important role in diagnosing and managing sight-threatening macular diseases such as age related macular degeneration (AMD) and diabetic macular edema (DME). By imaging the retina at micrometer resolution, OCT has given ophthalmologists the ability to visualize retinal structures in three


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dimensions. Yet, detailed analysis of OCT scans in clinical routine is time-consuming even for experienced physicians. With over 30 million OCT scans acquired annually worldwide and an increasing prevalence of chronic eye conditions, the human resources and expertise needed to assess OCT images, today and in years to come, are simply overwhelming.

Machine learning provides a pathway to automate inspections of medical imaging such as OCT scans. By using datasets of annotated examples, trained machine learning algorithms are not only faster at assessing scans, but also more cost effective when compared to human counterparts. These advantages have led to a surge of machine learning based methods for retinal image analysis. These include techniques that perform automated diagnosis, morphological shape estimation, treatment outcome estimation and clinical referral support. Broadly, these developments have hinged on clinical insights, novel machine learning techniques and large amounts of OCT scans.

In this context, biological markers, or biomarkers of the retina, have traditionally played a central role in both clinical routine and research. For example, monitoring fluctuations of fluid biomarkers using OCT is an essential part of the standard of care for managing chronic retinal conditions, while other biomarkers have been linked to how well patients respond to treatments. However, given that there are dozens of established biomarkers, their identification is both time consuming and challenging due to their number, size, shape and extent. Furthermore, other morphological markers yet to be identified may have a significant impact on patients' outcomes, needed treatment and prognosis.

For this reason, we investigated how an automated method we have designed can help us in identifying biomarkers reliably and help answer routine clinical questions (Figure 1).

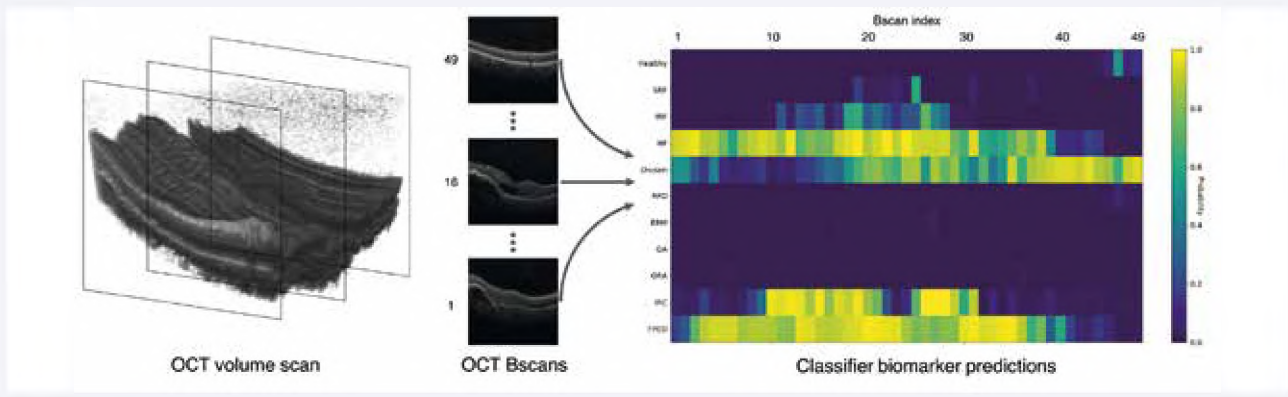

Figure 1: Evaluation of an OCT volume scan (left) using our proposed automated biomarker identification method. Individual cross-sections, or Bscans (middle), are processed and predictions on eleven biomarkers are given per cross-section (right). The color coding indicates the likelihood of a specific biomarker being present in a given cross-section.

To show this, we designed a machine learning method that automatically identifies a wide range of biomarkers in OCT scans that are routinely found in the clinical setting and research literature. Unlike recent trends in ophthalmology, our approach learns to identify biomarkers without needing to be shown where these are located in training scans, and obviates the need for burdensome segmentation annotations. That is, our method uses annotations that only relate to the presence of distinct biomarkers. Using a custom-built web-based annotator, gathering annotations can be done in parallel by multiple graders, and above all, in record time.

Our biomarker classifier – a custom convolutional neural network – was trained with 25,000 patient OCT Bscans and tasked with detecting which of 11 different possible biomarkers were present in a given Bscan. Coincidently, we noted that by forcing our network to evaluate Bscans and not volumes directly, our networks performance with OCT images from different devices remained high despite having somewhat different acquisition settings than the images used to train our method. By training our algorithm this way, our method was not only capable of identifying biomarkers more consistently than experienced experts in AMD and DME patients, but also allowed us to re-project what parts of the image data influenced the network's decision. The result of this is a series of class activation maps with a strong overlap of biomarker locations in the images (Figure 2) regardless of the size or extent of the biomarker present. Hence, even though our method was not explicitly trained with information as to what biomarkers look like, their appearance was learned from the data and allows for quasi-quantification and counting of biomarkers.

A consequence of this network and its ability to reliably identify biomarkers from different Bscans or Cscans by repeatedly evaluating OCT cross-sections, is its capacity to characterize patient data based on biomarkers. The case of fluid detection in clinical practice is particularly telling, where by aggregating sub-retinal fluid (SRF), intra-retinal fluid (IRF) and intra-retinal cysts (IRC), the automated detection of fluid in patients from the outpatient department at the Bern university eye clinic (Switzerland) was more concordant with expert graders than the attending physician. Similarly, we show that characterizing entire OCT datasets of patients is trivial, whereby allowing unstructured patient data to be categorized based on pathologies in a fully automatic way.

Generally, the trend of this work demonstrates yet again that AI systems, when trained with appropriate and sufficient data, can yield capabilities that rival that of expert ophthalmologists for well defined tasks. The

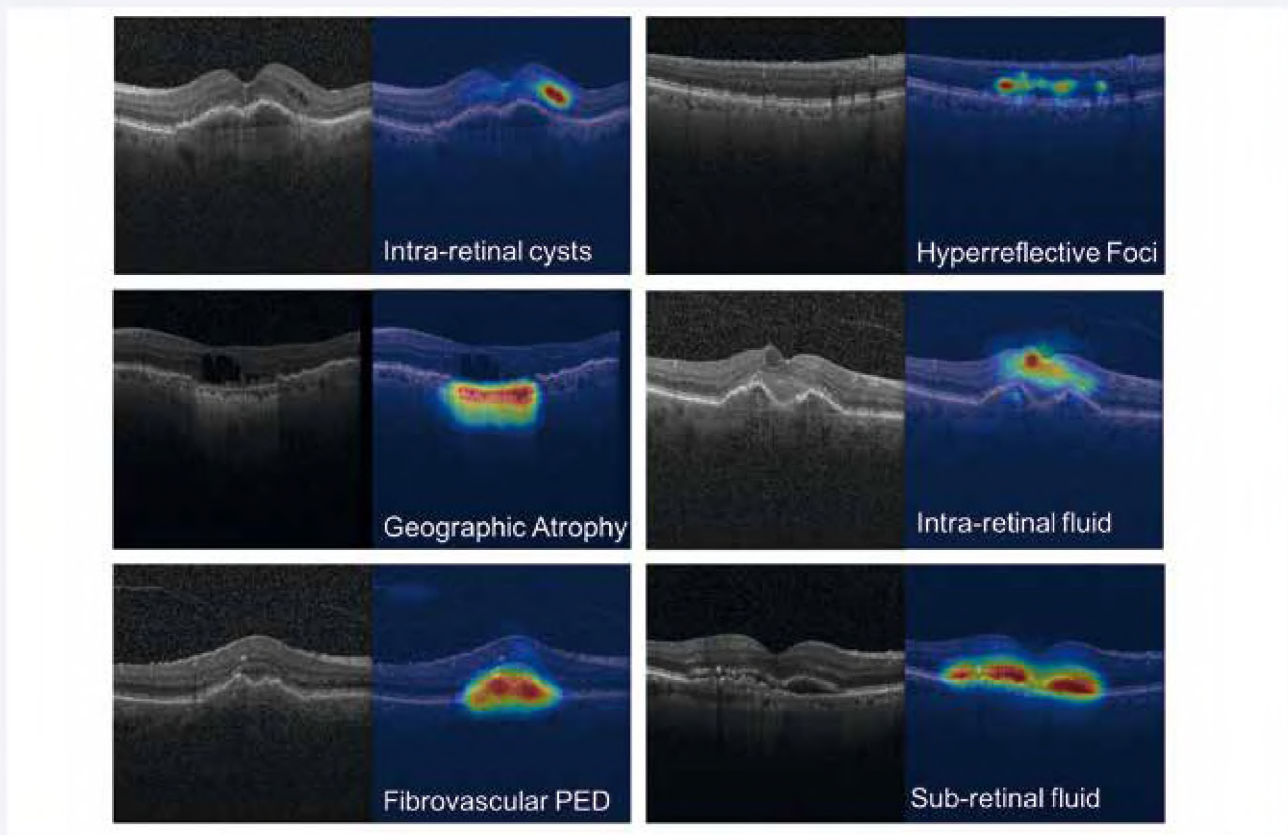

Figure 2: Classifier activation maps for different biomarkers on selected examples. Red regions illustrate regions of the image that are automatically found by our method to correctly predict the corresponding biomarker.

prospect of having such OCT analysis systems in the clinic and within reach of researchers has never been this close and will undoubtably become widely available in the near future. By then, the full extent of this technologies' impact will be made clear, perhaps through exciting discoveries and hopefully by improving clinical care. ■

EURETINA Session: AI in Retina
Thursday, 5.9.2019 **14.30 – 16.00**
Grand Amphitheatre

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