Early diagnosis of glaucoma

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Chronic open angle glaucoma is one of the top three causes of blindness in Europe, despite the fact that it is a disease that is easy to control in most cases. It is essential to reverse this trend and, to do so, efforts made by all the various health professionals must be coordinated [1].

It is acknowledged that the disease remains entirely unnoticed in its initial phase and that only early diagnosis can truly avoid progression towards blindness; this becomes almost inevitable when diagnosis is made in the final stages of the disease.

Over recent years strategies used to combat the disease have included screening programmes, information to the population, the identification of populations at risk and the distribution of information between the various links in the health chain, from the GP or family doctor through to hospital professionals, not forgetting, first and foremost, opticians and optometrists, who are in direct contact with the at-risk population.

In spite of all the efforts made, recent studies show that only less than 50% of patients with glaucoma have been diagnosed [2].

Screening campaigns. These campaigns are the subject of much debate. The methodology used is not unanimously approved, the sensitivity and specificity of tests are very low and the number of false negatives and false positives is very high. More effort is needed therefore to identify glaucoma in the populations considered as “suspect” during the campaign [3, 4]. We would also add here, in support of these campaigns, that it is certain that about half of all patients diagnosed as having glaucoma and treated by professional ophthalmologists, are not actually suffering from this disease [2]. Currently, most experts believe that detection campaigns are of use only to the at-risk population. Studies of this kind have nevertheless been used to assess the scale of the problem quite adequately and to determine prevalence amongst people aged 40 and over, which is between 1 and 4% in Europe, America, Asia and Australia, and between 1 and 8% in Africa [5, 6, 7].

Identification of the at-risk population

To improve the prognosis of glaucoma, it is important to focus on the at-risk population. However, if one wishes to obtain an appropriate result, training for ophthalmologists must be improved. They would then be in a position to identify true glaucoma in people with ocular hypertension, to avoid unnecessary treatments, taking account of factors such as life expectancy, the probable progress rate and other series of factors enabling the most appropriate action to be taken in each individual case [8]. Remember that, further to the popularity of early identification of glaucoma, it is estimated that...
about 50% of patients diagnosed after screening campaigns, are subjected to treatments that are unnecessary \[9, 10\]. Senility, family history, myopia, cardio-vascular disease and, to a certain extent, diabetes, are all risk factors amongst which it is recommended that priority action be taken due to a high rate of return in terms of diagnosis \[3, 4\]. However, the image analysis process, equipped with diagnosis algorithms, has greatly improved the detection capacity of campaigns and may lead us to reconsider diagnostic return rate in the future \[11\].

**Early diagnosis**

Methods currently used in diagnosis can be classified between “structural” methods and “functional” methods. The former are based on the hypothesis according to which it is possible to make a diagnosis more quickly by identifying damage to the optic disc or the layer of nerve fibres on the retina. The second category of methods attempts to measure functional damage.

**Procedures for the identification of functional damage**

1. Automatic perimeter: The appearance of the first automatic perimeters in the seventies was a real revolution in exploration of the visual field \[12\]. In 1979, the Octopus perimeter was recognised as being vastly superior to the Goldmann perimeter in terms of the detection of scotoma linked to glaucoma, which enabled earlier identification and better monitoring of glaucoma development \[13\]. Over the following years, diagnosis criteria were established and the development of probability scores began \[14\]. These achieved a high level of precision \[15\] and new algorithms appeared, which increased sensitivity and specificity \[16\]. More recently, in order to minimise errors that are the consequence of fatigue, new strategies have been developed to create quicker and more precise perimetry. These include the SITA programme for the Humphrey perimeter \[17\] and the TOP programme for the Octopus \[18\], which can be reproduced more easily and whose sensitivity and specificity are similar to traditional strategies (Fig. 1).
Fig. 1: *Octopus Visual Field (TOP Programme)*. In addition to the lesion shown by the colour code, the instrument presents the digital value of sensitivity, the difference compared to the normal, corrected difference according to age and the Bebie curve (from left to right and from top to bottom).

To achieve earlier diagnosis, new perimetric examinations are appearing. They tend to direct research towards the neurons that are supposed to be damaged in the initial phases of glaucoma. Short wave perimetry (SWAP) has been developed [19], which detects damage 3 to 4 years ahead of traditional examinations [20]. Frequency doubling perimetry has diagnosis sensitivity that is below that of conventional perimetry, but it is nevertheless extraordinarily useful as a screening tool, thanks to the speed at which results are obtained and the fact that the instrument is very easy to handle [21]. Finally, mention should be made of pulse perimetry, which not only detects defects linked to glaucoma at an early stage, but also benefits from a high degree of reproducibility [22].

2. Electroretinogram and visual evoked potential: On a theoretical level these are processes recognised as being able to detect damage linked to glaucoma [23, 24], but if we attempt to apply them to early diagnosis, they have not, to date, shown proof of any great diagnostic capacity.

**Procedures for the identification of structural damage**

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1. Ophthalmoscopy of the optic disc and of the nerve fibre layer: Analysis of the disc in binocular vision, specifically using a slit lamp with adapted converging lenses or contact lenses, enables an expert to identify early any damage linked to glaucoma. Analysis of the fibre layer using appropriate filters is used to detect areas of atrophy, including amongst patients in whom no perimetric damage has been detected. These two examinations offer a high diagnostic return rate for glaucoma experts, but results cannot be extrapolated to general ophthalmologic practitioners [25, 26, 27].

2. Photography of the disc: The characteristics of the normal disc [28] and of the peripapillary region have been defined extremely precisely and stereoscopic photography is used to obtain a more precise diagnosis. However, the difficulty referred to in the previous paragraph remains: only an expert will have the degree of precision required to give a true early diagnosis. Indeed, the number of false positive patients detected by ophthalmologists in general practice is extremely high. Planimetry is used to perform extremely precise quantitative studies, but this is a process that has been overtaken, in practice, by new technologies.

3. Photography of the retinal nerve fibre layer: Photography of the retina with a monochrome light of 475 to 520 nm is used to perceive contrast on the dark base of the retinal nerve fibre layer and to detect the slightest defect [29]. Application of digital technology to photography is used to view the shots taken immediately. Such progress has improved the clinical usefulness of this examination, which requires the use of a retinograph only [30].

4. Confocal tomography by laser scanning (HRT): This examination is used to obtain three-dimensional images of the retina and the optic nerve [31]. The most important clinical application of the Heidelberg retinal tomograph (or confocal laser) is without doubt the analysis of the quality of the glaucomatous disc. Its reproducibility is greater than planimetric examinations applicable to photography, particularly the HRT3 version. It has two programmes (Moorfields and Glaucoma probability score or GPS) used to compare the disc with that of a normal eye in a person of similar age and race. This makes it easier to use by ophthalmologists in general practice who are not glaucoma experts and its diagnosis return rate is high. The instrument performs three scans of 64 images using two combined pinhole apertures. Its light source is a red diode 670 nm laser that is used to build up a three-dimensional image from which the measurements are taken. To obtain the measurements the operators must position the line of the limit of the optic disc correctly because otherwise errors can occur [32, 33]. We should note, however, that this stage is not necessary to obtain a result with the GPS programme. Variations in intra and inter-observer measurements are highly acceptable [34], making this an extremely useful instrument both for early diagnosis and for surveillance of glaucoma progression (Fig. 2).
5. Optical coherence tomography (OCT): The instrument projects a 820nm ray of light onto the retina and compares the reflections obtained on the retina with those obtained by the reflection of light on a control mirror. It obtains data from a total of 1024 points on the retina and the optical nerve and then gives a cross section image of the retina and the optic disc. These results are used to assess the thickness of the retinal nerve fibre layer \[35\] with extreme sensitivity and precision \[36\]. Also, the programme that analyses the optic disc and which is used for early detection of glaucoma does not require the positioning of the control plane; this is a great advantage for ophthalmologists in general practice \[37\]. Reproducibility of measurements is very good \[38, 39\]. New versions of OCT that have recently been put on sale offer greater precision and even better reproducibility of measurements (Fig. 3) \[40\].

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6. Laser polarimetry (GDx): The retinal nerve fibre layer acts like a birefringent structure. This birefringence can be measured \([41]\) by a light that crosses the retina twice. During its return route it is subject to a change in polarisation that leads to a delay in the transmission of light. Such delay is directly linked to the thickness of the medium crossed, that is to say of the nerve fibre layer \([42, 43]\).

The instrument uses a 780nm diode laser as its light source, which crosses a polariser and a polarisation modulator and is then projected onto the retina. This is where it is subject to the transformations described above. One then obtains 65536 items of polarisation data in a field of 250x250 pixels. Optimum measurements are achieved in a circle of 1.75 papillary diameters located in parallel at the edge of the disc, the place where the fibre layer is most even, which allows for the most adequate degree of polarisation. The instrument has a system that allows for cancellation of polarisation of the other ocular structures. This difficulty has been dealt with in the latest versions of the device, thus improving its reliability. The VCC model is currently the most widely used. Its reproducibility, sensitivity and precision have been particularly improved \([44, 45, 46, 47]\).
Fig. 4: GDx VCC graph. Verification of the existence of an impact in the network of upper and lower fibres in the right eye and upper in the left eye.

The future

If we can create awareness amongst the at-risk population that they need regular ophthalmologic monitoring, if we apply the technological progress that was achieved over the closing years of the last century appropriately along with the improvements seen during the current decade, we can then achieve the objective sought of diagnosing the 50% of under-diagnosed glaucomas in the so-called developed countries. Careful anamnesis by health professionals, opticians, optometrists and ophthalmologists, as well as regular, rigorous and adapted research, in compliance with the standards laid down by the World Health Organisation, will enable us to achieve this objective in the near future. A minimum contribution by each one of us, combined with that of many others, will enable us to develop this early diagnosis for all.

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