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Validity and cost-effectiveness of methods for screening of primary open angle glaucoma

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Health political background

Glaucoma is a progressive disease of the eye, which may lead to visual impairment or blindness if undiagnosed and untreated. About 950000 people are affected by primary open angle glaucoma (POAG) in Germany, an estimated 50 % of which are undiagnosed. Glaucoma is the third commonest cause of blindness in industrialised nations. In Germany about 16500 persons are registered blind in both eyes due to glaucoma and receive blindness allowance. According to other sources an estimated 50000 persons are blind due to glaucoma. The German Opthalmological Society (DOG) and the German Association of Ophthalmologists (BVA) recommend a screening for glaucoma according to their guidelines for all persons between the ages of 40 to 64 in a triennial interval and for persons over the age of 65 in annual to biannual intervals. The Federal Joint Committee (G-BA) disapproved the introduction of a glaucoma-screening program on expense of the compulsory health insurance in December 2004 because of insufficient valid data on test procedures and combinations of tests, age limits and screening-intervals as well as insufficient data on early treatment of glaucoma on the criteria “prevention of blindness”. Currently charges of examinations for early detection of glaucoma are only borne by compulsory health insurance in case of suspected early symptoms or if certain risk factors are prevalent. Otherwise the costs of about 16 to 20 EURO of an examination for glaucoma (including Anamnesis, ophthalmoscopy and tonometry) have to be borne by the patient.

Scientific background

Glaucoma is a group of optic neuropathies that have in common a degeneration of retinal ganglion cells and their axons. POWG is the most common form. Increased ocular pressure is today recognised as one of several risk factors. It is found independent of glaucoma as “ocular hypertension”. On the other hand, glaucoma can be diagnosed independent of increased ocular pressure, which is termed “normal tension glaucoma”.
The diagnosis of Glaucoma is based on the evaluation of the optic disc, retinal fibre layer and visual field. Morphological changes of the optic disc and retinal fibre layer are analysed by ophthalmoscopic evaluation (including fundus photography and nerve fibre layer photography), the confocal scanning laser tomography (usually with the Heidelberg Retinatomograph), the scanning laser polarimetry (GDx), the retinal thickness analysis and optical coherence tomography. Scotomas are diagnosed by perimetry. In addition to the standard automated perimetry, methods such as frequency doubling perimetry (FDT) and short wavelength automated perimetry can detect glaucoma earlier. Intraocular pressure, the most important treatable risk factor, can be measured by tonometry.

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Clinical signs of glaucoma are subtle, the disease progression is slowly progredient and already existing visual loss can not be reversed. Therefore, early diagnosis and screening are essential components from a medical point of view.

Research questions

Following research questions are posed: What is the diagnostic validity of screening-tests for POAG, as well as for two other forms (pigmentary glaucoma and pseudoexfoliation glaucoma, which are related to POAG concerning diagnosis and therapy)? Which risks are associated with these screening-tests? Are screening-tests for POAG cost-effective? Which ethical and legal issues are associated with a screening for POAG? The questions are posed with respect to the use in a screening setting in Germany.

Methods

This HTA-report follows the method of a systematic review. Out of 2602 abstracts yielded by a systematic literature research in 35 international databases (DIMDI HTA-Superbase and Cochran-Databases, October 2005) 55 studies were included for medical assessment, three publications were included for the economic assessment (one double count with medical literature) and two articles remained for the ethical discussion after a two-stage selection process according to predefined criteria. For the discussion of legal aspects relevant juridical texts were included.

Results

Out of 55 medical articles related to the research question, eight primary studies investigate only perimetric methods, nine confocal scanning laser ophthalmoscopy and eight scanning laser polarimetry. One of these methods is being investigated in combination with other methods in 13 primary studies and eleven articles analyse several other methods. Six systematic reviews or HTA-Reports were used. The majority of studies is based on patients investigated at universities and therefore the quality of the papers is generally low, as far as the evidence in respect of screening is concerned. However, also studies performed under screening conditions have methodical limitations.
Out of eight articles investigating perimetry by FDT only or in combination with other perimetric methods, only one study was performed as a public screening. In this study FDT has a sensitivity of 92 % and a specificity of 93 %. Another study uses a non-mydriatic fundus camera in combination with FDT for screening in a general population. The sensitivity for FDT in relation to the camera is 58.6 % and the specificity is 64.3 %. The screening study with the best quality finds sensitivities between 78.9 and 84.2 % and specificities between 55.0 and 65.7 % depending on the threshold used. Studies investigating clinical populations show sensitivities between 29 and 100 % and specificities between 81 and 100 %.
No study could be found evaluating only scanning laser tomography in a screening setting. In the available studies with clinical populations sensitivities for the HRT are between 26.5 % in preperimetric and 97 % in perimetric glaucoma patients. Specificities lie between 65 and 95 %. The above mentioned screening study (including also FDT) with the best quality shows sensitivities between 89.5 and 94.7 % and specificities between 80.6 and 90.5 % for the HRT depending on the threshold used.
There are only two studies evaluating scanning laser polarimetry under

screening conditions. In a study with medium quality using a modulation parameter the optimal sensitivity is 86 % and the specificity is 90 %. The second study is of lower quality and only a sensitivity of 82 % is reported. Studies investigating clinical populations have sensitivities between 62 and 100 % and specificities between 73 and 100 %.
No single method exists with both, high sensitivity and high specificity for screening purpose. The results of all studies investigating several methods show uniformly that sensitivity, specificity and receiver operating characteristic (ROC) curves (showing sensitivity and specificity graphically) can be improved by combining methods and using adequate algorithms. This is also true for others than the reported methods.
The advantage of a sequential diagnostic is confirmed by a qualitatively high Australian screening study. Using simple methods (visual acuity, family history of glaucoma, FDT) in a first stage reduces the number of participants by 59.3 %. The second stage (scanning laser tomography) is only performed when results of the first stage are pathological. The optimal screening strategy combing visual acuity, family history of glaucoma, FDT and HRT has 96.8 % and 89.7 % sensitivity and specificity, respectively.
Systematic reviews and HTA-reports do not give evidence based recommendations for screening of glaucoma. A Canadian HTA-report concludes that the evidence is not sufficient in order to recommend or reject a general screening for ocular hypertension or POAG. Regarding the risk of the examinations, only eye drops or methods having direct contact with the cornea comprise a small risk for adverse events.
Out of seven publications relevant for the economic assessment, two economic models (three publications) on cost-effectiveness of screening-tests could be identified, which have a good quality.
A British cost-effectiveness analysis published in 1997 calculates cost per true positive for various combinations of the three main tests ophthalmoscopy, perimetry and tonometry and associated referral criteria in a primary care setting. The study assumes a prevalence of 0.6 % of previously undetected glaucoma in the screening-population and calculates one screening-cycle. The combination of ophthalmoscopy and tonometry for all persons screened and perimetry as an initial test only for persons at high risk (or for all persons) shows at a sensitivity of 80 % (87 %) a cost-effectiveness ratio of 1745 USD (2057 USD) per true positive diagnosis, including all direct costs of diagnosis. Both above mentioned screening-modes show a specificity of ≥ 97 %. A screening is most economic, if it is conducted as a part of a general eye examination (“case-finding”) thus the cost of the ophthalmoscopy and overhead-cost could be minimized. Furthermore costs could be reduced if tonometry (non-contact tonometry) and / or perimetry would be performed by non-ophthalmologically trained assistants.
A Canadian HTA-report published in 1995 models the cost per year of blindness avoided, thus considering costs of diagnosis and treatment as well as benefits from blindness avoided. In 14 scenarios different combinations of screening-examinations (primarily funduscopy and tonometry as an initial examination and perimetry as a secondary test), screening-intervals, age-limits and rates of participation, compliance and effectiveness of treatment are considered. From a government perspective (Quebec) a screening of persons aged 40 to 79 in an interval of three (five) years, with an assumed participation and compliance rate of 75 % each and an assumed effectiveness of treatment of 50 %, could avoid 354 years of blindness, which corresponds to a cost-effectiveness ratio of 100000 CAD (78000 CAD) per year of blindness avoided. Years in partial blindness, which might be prevented by a glaucoma screening and subsequent treatment, are not considered in the outcome-parameter. The authors of the Canadian HTA

report conclude that because of a high degree of uncertainty with respect to benefits and the high costs involved, the setting-up of a glaucoma-screening program cannot be supported.
No economic evaluations of the most recent methods (as described in the medical assessment of this HTA) can be found in the published literature.
Two cost-analysis of screening-programmes in different settings (a low cost screening conducted by non-medical students and a screening conducted in the out-patient department of a university hospital) do not describe transparently all costs incorporated in the analysis, furthermore they are only of minor relevance because of the specific setting used.
Only two articles considering ethical aspects of a screening for POAG could be identified by the literature search. No further relevant publications could be identified by hand search.
Both articles discuss the benefits of glaucoma screening and treatment on a general basis. Amongst other it is discussed that there are no studies with clear endpoints (blindness) for the appraisal of glaucoma screenings. According to WHO criteria it is necessary for a screening that such studies exist.
From a juristic point of view it is important, that some medical examinations which are relevant for the detection of glaucoma (like the tonometry) are only reimbursed if certain risk factors or definite suspicious findings exist. However, there is a wide scope in the interpretation of this risk factors.

Discussion

For the detection of POAG (as well as pigmentary glaucoma and pseudoexfoliation glaucoma, which are related to POAG concerning diagnosis and therapy) several methods of investigation can be used. However, the evaluated literature shows that no single method, but also no combination of methods is presently established for screening of glaucoma. The number and quality of the studies is presently not sufficient to allow the recommendation of a method or a combination of methods. Studies on early diagnosis and screening of glaucoma include most commonly FDT as a perimetric method and confocal scanning laser tomography and scanning laser polarimetry as morphologic methods. The establishment of morphologic methods for glaucoma screening can be more elaborative because morphologic changes can occur at an early stage, at which part of the standard diagnosis (standard perimetry) can still be normal. Therefore longitudinal studies have to be performed in order to confirm that early morphologic changes are related to glaucomatous visual field defects at a later stage.
One of the few population based studies with sufficient quality has good results regarding sensitivity and specificity using simple methods such as visual acuity and family history of glaucoma. Such parameters are rarely investigated in the available studies but could also be used in screening programs, as well as an ophthalmologic examination and tonometry. An essential part of the above mentioned screening study is the sequential course with simple methods at a first stage and more complex methods at a second stage.
From an economic perspective no recommendation for a single screening test or combination of screening test can be given. Currently no economic evaluations of the more recent methods such as FDT or scanning-laser-polarimetry are published. Economic Evaluations assessed consider ophthamalmoscopy, perimetry and tonometry or combinations of these in the context of the British and the Canadian Health system; an adaptation of the results to the German health care system has to be critically assessed.
A screening-pathway, as recommended by the BVA and DOG in their

Guideline 15c on the detection of glaucoma, shows a lower sensitivity at higher cost per true-positive diagnoses from the perspective of the British National Health Service, than a screening mode including perimetry for patients at risk in the initial examination. The Canadian evaluation calculates cost per year of blindness avoided; the study authors conclude that because of the high degree of uncertainty and because of the high cost no support for a formal glaucoma screening program can be given.
With respect to a comparison of screening-tests or combination of these the intermediate parameter cost per true-positive diagnosis is appropriate. An economic evaluation of a glaucoma-screening, aiming at morbidity-related outcome-parameters, should not only consider the effects on blindness, but also on visual impairment.
From current projects assessing (the medical and) economic effectiveness of screening for glaucoma (e. g. by the “National Coordinating Centre for Health Technology Assessment” (NCCHTA)) evaluations of more recent screening-test might be expected.
From an ethical and juristic point of view the unclear situation concerning reimbursement of medical examinations which are relevant for the detection of glaucoma (like a tonometry) could be a problem especially for poorer classes of population. The decision if such a medical examination is reimbursed by the GKV or not, depends highly on the argumentation to the GKV of the doctor or the patient.

Conclusions / Recommendations

Presently neither a single nor a combination of methods can be recommended with sufficient evidence for the detection of POAG. The diagnostic validity of single methods is not high enough. A useful combination would be a functional test (such as FDT) together with a morphologic method (such as an ophtlamologic ecxamination, confocal scanning laser tomography or scanning laser polarimetry). Tonometry has been used earlier, but can not be used solely because of its poor sensitivity. However, it could be a useful part of a screening algorithm because of its high specificity. Simple methods such as visual acuity and family history of glaucoma could also be part of such programs.
Future studies have to evaluate the optimal combination and order of methods. High sensitivity and specificity are not the only relevant parameters for establishing screening programs. An improved management of patients is also essential, which can only be reached by randomised controlled intervention studies with visual parameters as end points.
No final conclusions can be drawn with respect to cost-effectiveness of glaucoma-screening methods from the published literature or by adapting the results of published economic evaluations to the German context. An economic evaluation of a screening-programme should consider the fact, that by screening for glaucoma other eye diseases could be detected early, which might yield medical and economic benefits. Furthermore an economic evaluation of a clinically effective screening-method should consider the effects of blindness avoided, as well as effects on the prevention of visual impairment.