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Some clinical implications of the collaborative normal tension glaucoma study

Badania wieloośrodkowe jaskry z niskim ciśnieniem – implikacje kliniczne

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Summary: This is to present the results of randomized multicenter normal tension glaucoma study. The primary aim of the study was to establish whether a 30% or greater pressure reduction altered the course of NTG compared to untreated controls. Our study confirms that in glaucoma patients even with normal intraocular pressures the pressure is involved in its pathogenesis and that pressure reduction favourably affects its course in a significant proportion of cases. Moreover, it identifies a great variability of the untreated disease. Over 7 years nearly half appeared to show no progression, the other half showed progression of their damaged area but this was slow and often did not result in a change of their MD index. There was a small group, who showed rapidly advancing disease, which was likely lead to visual handicap. Moreover, it was then attempted to study risk factors, other than intraocular pressure. Gender, ethnic background, migraine and the presence of disc hemorrhage adversely influence the course of the disease and may therefore account for some of the variability in the course of the disease.

Key words: normal tension glaucoma, randomized multicenter study.
Słowa kluczowe: jaskra normalnego ciśnienia, wieloośrodkowe badania randomizowane.

Although Chronic Glaucoma has been recognized for at least 150 years particularly since the discovery of the ophthalmoscope and the early plotting of the central visual field, it is worth remembering that almost all of the glaucoma manifested itself with symptoms of which pain, often of sudden onset, were the commonest. Routine examination of the eye was a much later development.

One should therefore not be surprised that the literature dealing with glaucoma until the end of the second world war dealt with angle closure and secondary glaucoma which included neovascular glaucoma as well. The separation of chronic open angle glaucoma and angle closure glaucoma was only 30 years old and in the 1980s we were unaware of the influence of pressure lowering in NTG and even the value of pressure reduction for Chronic Open Angle Glaucoma was challenged.

Automated perimetry with rather elementary programmes came into existence in the early 1980s which made it possible to design a randomized multicentre study of the effects of pressure reduction on the course of Normal Tension Glaucoma (NTG).

In order to qualify for inclusion into the study patients had to have glaucomatous field defects and an optic nerve which had features of the disease. Ten intraocular pressure readings (6 on the same day throughout the day) with a median of less than 20 mmHg. And no reading above 24 mmHg. In fact there were no reading above 21 mmHg in those recruited. A fairly comprehensive history of systemic disease was obtained. The visual field damage had to be not too severe, so as to be able to follow progression, and the better eye was chosen for the study. Patients were followed every 3 months with assessment of vision, intraocular pressure measurement, visual field plotting and ophthalmoscopic examination of the disc. When progression of the visual field damage or disc damage was identified or the appearance of a disc hemorrhage took place, the study eye was randomized to pressure reduction (30% or more) by medical means with pilocarpine and/or laser trabeculoplasty or surgical fistulisation or to no treatment. Patients who threatened fixation in the study eye were randomized immediately. Fresh baseline fields were plotted after pressure reduction had been obtained and the patients were again followed 3 monthly until an "end point" was reached when further progression was found. A new hemorrhage did not constitute an end point (1).

The primary aim of the study was to establish whether a 30% or greater pressure reduction altered the course of NTG compared to untreated controls. 230 eyes were recruited and 145 were randomized having progressed or having a perceived threat to fixation. 5 eyes randomized to pressure reduction failed to achieve this and were left out from the analysis of the influence of pressure reduction on the course of the disease, because they failed to have their pressure reduced adequately (1).

It became clear that after 2 or 3 years the survival of the treated eyes was significantly better than that of the untreated controls (fig 1).

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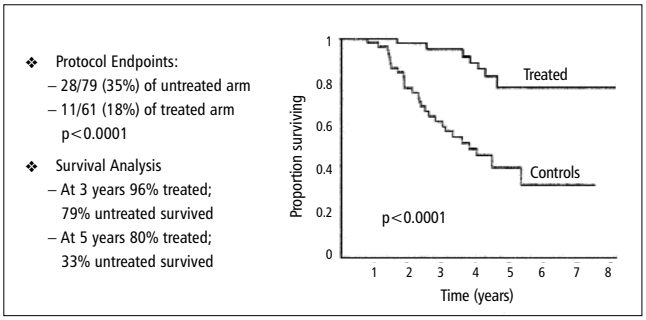

Fig. 1. Survival curves of untreated controls and treated patients from randomization.

We developed and tested a computer method to assess progression demanded by our study protocol and we were therefore able to use the study as a clinical trial posing the question, as to whether patients benefited from pressure reduction. For the clinical trial progression was measured from the time of randomization in all the 145 eyes that were randomized (2).

To our astonishment the KM survival curves failed to show statistical differences between the two groups (fig 2). It gradually became clear that the surgically treated eyes developed cataracts more frequently than the medically and laser treated eyes which behaved more like the untreated controls. Once the information from all cataract eyes which reduced vision by 2 Snellen lines was censored at the time of the diagnosis of the cataracts, the survival curves showed the same significant difference between the treated and the untreated eyes (fig 3).

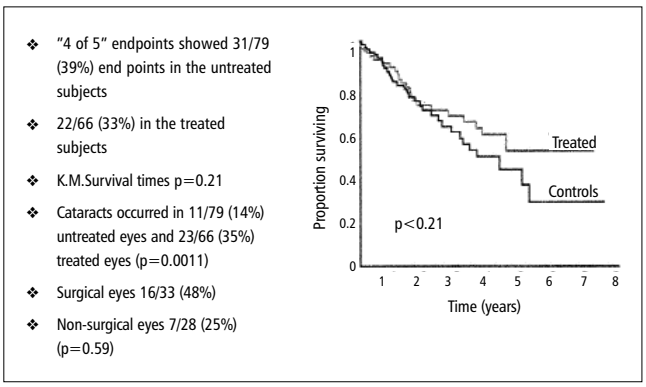

Fig. 2. Survival curves of endpoints in untreated controls and treated patients from visual field baselines obtained at randomization.

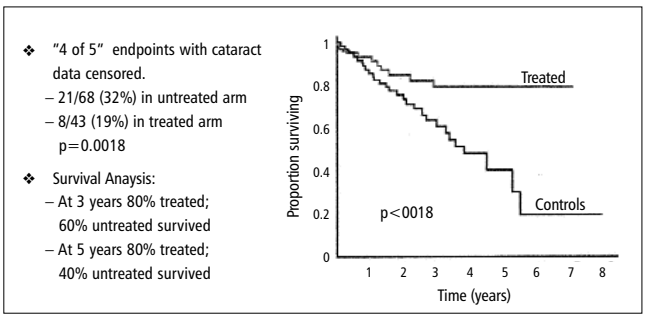

Fig. 3. Survival curves of endpoints in untreated controls and treated patients from visual field baselines obtained at randomization with data of eyes developing cataracts censored at the time of the diagnosis of the cataract.

It was concluded from these two studies that pressure reduction influences favourably the course of NTG and is therefore involved in its pathophysiology. It was also clear that when one excluded cataract formation the treated eyes benefited from the pressure reduction. It appeared that those eyes randomized because of a threat of fixation had a similar course to those in whom fixation was not initially threatened. Close to 20% of eyes whose intraocular pressure was reduced continued to progress while 30% of those eyes untreated did not progress over 5 years.

The study probably presented the first opportunity to study untreated NTG eyes in those who were randomized to no treatment, and in those who were never randomized. In 160 such eyes the course of their disease was very variable. Over 7 years nearly half appeared to show no progression, the other half showed progression of their damaged area but this was slow and often did not result in a change of their MD index. There was a small group who showed rapidly advancing disease which was likely lead to visual handicap (fig 4).

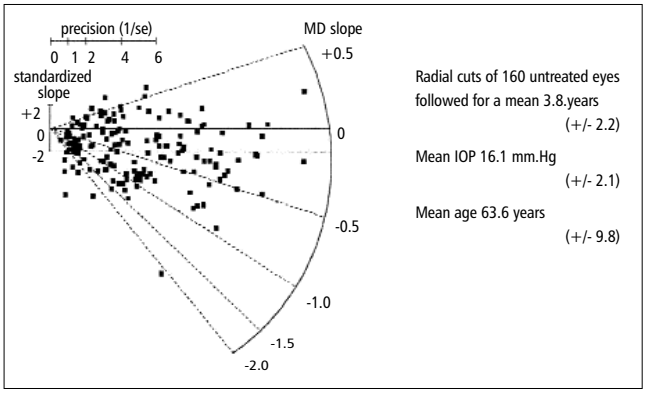

Fig. 4. Radial plots representing the estimated slopes of the MD index of all untreated eyes regressed on time (dB per year). Points situated farther from the center of the circle represent slopes that are estimated with greater precision. Points along the same radius of the circle have the same slope value, as labeled along the circumference. Points below the horizontal dotted line at the level marked at the center as –2 standardized slope represent statistically significant negative slopes ($p<0.05$).

It was then attempted to study risk factors, other than intraocular pressure, which might help to explain the great variability in the course of the untreated disease in these eyes. We found that the KM survival slopes were more marked in women than in men (fig 5), in patients with a history of migraine as opposed to those without such a history (fig 6). Patients with a disc hemorrhage on entry into the study showed a significantly steeper survival curve when compared to those without such a baseline hemorrhage (fig 7). Our Oriental patients showed a lesser progression compared to Caucasians. There were only a few Afro-American patients in the study and no statistical analysis of their course was possible (4).

In view of the risk factors identified the clinical trial was re-analyzed separately for men and women. The beneficial effect of pressure reduction was strongly positive in women but negative in men. This raises some interesting questions, not the least of which is the identification as to what accounts for the difference between males and females with regards to the effects of pressure reduction.

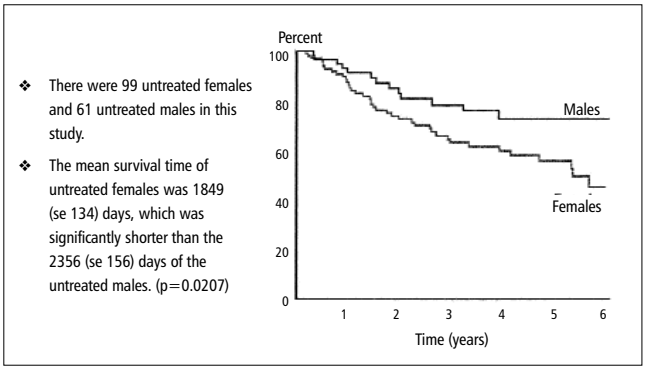

Fig. 5. Kaplan Meier curves comparing males and females and females with respect to time first reaching demonstrable progression.

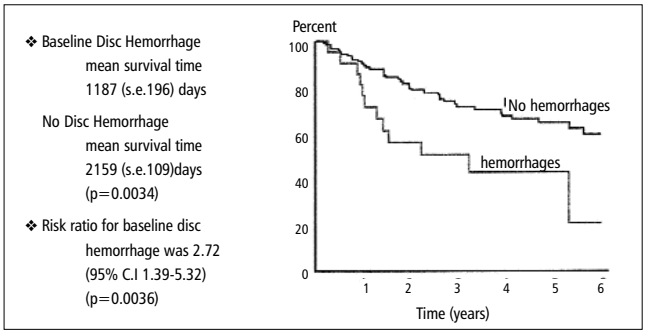

Fig. 7. Kaplan Meier curves comparing those who had or did not have a disc hemorrhage on the initial qualifying examination with regard to the time of first reaching demonstrable progression.

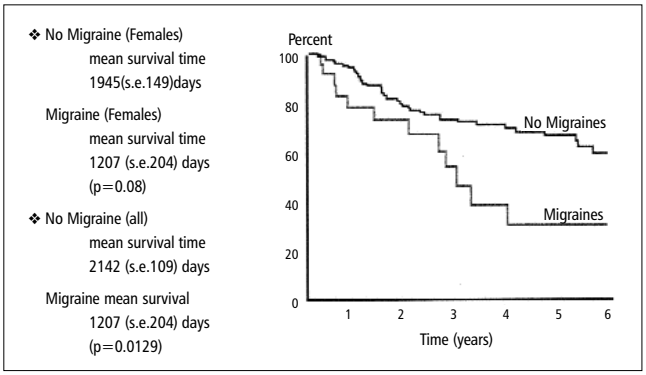

Fig. 6. Kaplan Meier curves comparing females with and without migraine with regard to time of first reaching demonstrable progression.

The apparent lack of a gender difference in the Scandinavian EMG Trial suggests that there may be some acquired differences as opposed to genetic differences between North American and Scandinavian women which might have clinical applications.

Having ascertained some of these possible risk factors we went back to the randomized patients to see whether the effect of pressure reduction differed in the subgroups with and without those and other possible risk factors (5). The number of subjects was sufficient to answer the original question of whether IOP reduction influenced the course of NTG. In the present analyses, directed at studying whether the effect of IOP reduction was different in the presence or absence of various traits, the subgroups were of course smaller, at times leading to insufficient power to show strong statistical significance, but enough to suggest a plausible impact of certain traits that deserve further investigations. In order not to discard differences of potential importance, we did not adjust the p-values for multiple comparisons. It should be noted however, that a number of risk factors or traits did demonstrate highly significant differences, and large estimated differences for which a small size of the subgroup may have caused equivocal statistical significance should not be dismissed.

The course of the disease in women showed a better response to pressure reduction than men (tab. I.). Patients without a disc hemorrhage, on entry to the study, had a better response to pressure reduction than those with (tab. II.). Those with a family history of glaucoma had a better response than those without such a history. Patients without a family history of stroke and those without a history of cardiovascular disease showed a better response to pressure reduction than those who had those traits (tab. III.). It was impossible to ascertain whether migraine had a different response from lack of migraine because migraine, in our study, occurred almost entirely in women and the good response in them to pressure reduction could not allow us to interpret the migraine component of their response to pressure reduction (tab. IV.).

Females benefit from IOP reduction while males appear to benefit much less.

Risk factor		Untreated			Treated			p
		n	mean	se	n	mean	se	
Gender	Females	47	1776	185	47	2663	209	0.0063
	Males	29	1922	233	17	2075	185	0.3122

Tab. I. Comparison of survival to progression expressed in days of males and females treated and untreated.

Patients with no disc hemorrhage benefit from IOP reduction while those with a hemorrhage do not.

Risk factor		Untreated			Treated			p
		n	mean	se	n	mean	se	
Hemorrhages	Present	12	1533	343	11	1829	250	0.3051
	Absent	62	1882	153	50	2738	192	0.0164

Tab. II. Comparison of survival to progression in days of patients treated and untreated with and without a baseline disc hemorrhage.

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Patients with F.H. of glaucoma benefit from IOP reduction while those without do not.
Patients without a F.H. of stroke and patients without cardiovascular disease benefit from IOP reduction, while those with those traits do not.

Risk factor		Untreated			Treated			p
		n	mean	se	n	mean	se	
Family history Glaucoma	Absent	47	1949	186	36	2098	144	0.2927
	Present	26	1677	277	27	2977	317	0.0055
Family history Stroke	Absent	57	1788	166	42	2813	208	0.0024
	Present	17	1795	222	17	1948	249	0.4893
Cardiovascular	Absent	38	1385	129	30	2245	135	0.0014
	Present	38	2142	198	34	2582	230	0.4517

Tab. III. Comparison of survival to progression expressed in days of patients treated and untreated with and without a family history of glaucoma, a family history of stroke, the presence of cardiovascular disease or an absence of these traits.

Females with and without migraine benefit from IOP reduction.

Risk factor		Untreated			Treated			p
		n	mean	se	n	mean	se	
Migraine (females only)	Absent	37	1884	197	40	2705	233	0.0185
	Present	10	745	114	7	1960	515	0.0491

Tab. IV. Comparison of survival to progression expressed in days of females treated and untreated with and without the presence of migraine.

Whether IOP reduction in females fully overcomes additional risk posed by migraine is not clear.

Our study confirms that in glaucoma patients even with normal intraocular pressures the pressure is involved in its pathogenesis and that pressure reduction favourably affects its course.

It identifies a great variability of the untreated disease. While the disease progresses in half the untreated eyes over a 7 year period the progression is slow and it often fails to significantly change the MD index over time. In a small group of patients the disease progresses quickly and in these patients, if the disease was bilateral, visual handicap would be very likely. Gender, ethnic background, migraine and the presence of disc hemorrhage adversely influence the course of the disease and may therefore account for some of the variability in the course of the disease.

The differences in the effects of intraocular pressure reduction on the presence or absence of some of the above traits and others needs to be refined in future studies. The finding that patients with ischaemic heart disease, with a history of stroke and those with disc hemorrhage do not seem to benefit from pressure reduction, while those without these traits do suggests that patients with some vascular occlusive disease may have a disease which is less pressure sensitive and possibly in them pressure may not be a factor at all. This was suggested by previously reported findings (6). If there is a form of glaucoma in which intraocular pressure is not a factor, these patients are likely to form a greater proportion of patients with so called normal tension glaucoma than in those in whom the pressure is markedly elevated.

Having presented the findings of the NTG study as presented on behalf of all the collaborators I can now present some personal observations which I think already have clinical implications for the management of patients with this disease. Pressure reduction appears to benefit these patients, particularly in women with and without migraine. Women with migraine appear to have the most severe course of the untreated disease. Whether men as a group benefit is much less likely. One has to remember however, that statistical does not mean that in all women there is a precipitous progression of their disease nor do all men behave as benignly as the statistical study suggests. The treatment has therefore to be individually appropriate for the patient. The study also suggests that most untreated patients with NTG progress slowly. It is probably wise to establish a few baseline fields to identify those who appear to progress rapidly, while in the others a more conservative attitude is not out of the place. The risk factors for the variability of the course of the untreated disease, so far identified, does give a lead as how an individuals disease might unfold. The fact that patients with fixation threats appear not to behave differently from those without such a threat would suggest that they too might benefit from establishing their individual pattern of progression but the more severe consequences if they belong to the rapidly progressing group requires clinical judgment. The perimetric central programme 10-2 or others, will show that in some of these patients the threat to fixation is much closer to fixation than others (7). The interesting finding that patients with cardiovascular disease, those with a family history of stroke and those with a disc hemorrhage appear to respond less to pressure reduction, suggests to me that these traits might indicate that in these groups the disease is less pressure dependent (and possibly even pressure independent) which may have some management implications particularly, if they continue to progress when the pressure has been significantly reduced by treatment. It is possible that in them the disease progresses due to the factors other than intraocular pressure.

I believe that our studies and those of others also teach us that dividing the disease into NTG and COAG by an arbitrary pressure level is simplistic and possibly counterproductive. Chronic Open Angle Glaucoma is a chronic optic neuropathy with many risk factors, some of which are now finally being recognized. In the future when we are able to reliably identify the mix of risk factors in individual patients, many of which still need to be identified, we will start to manage the disease more rationally, we will establish a more accurate prognosis for individuals and we should improve the risk/benefit ratios for our interventions.

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