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Aspirin effect on cataract formation in patients with rheumatoid arthritis alone or combined to diabetes

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Abstract

The prevalence of cataracts is significanly lower in patients with rheumatoid arthritis receiving aspirin (mean of 2,700 mgs daily for an average of 10.4 years) as compared to a matched population not receiving aspirin. Similarly, fewer cataracts were found among a population with diabetes and rheumatoid arthritis receiving aspirin (mean of 2,340 mgs daily for an average of 8.8 years) as compared to a matched population on no aspirin. The effects of aspirin on cataract formation may result from 1) lowering of plasma tryptophan levels and increased excretion of tryptophan metabolites, 2) inhibition of aldose reductase and sorbitol formation in the diabetic lens, 3) inhibition of tryptophan or kynurenine binding to lens protein.

Introduction

The widely disseminated concept that cataracts are found in most humans after age 65 years is erroneous. Actually, cataracts were found in only 13% of the 65-74 year old and 41.4% of the 75+ year old populations by the criteria of the Framingham Eye Study (FES) (14). Furthermore, in the FES lens changes such as vacuoles, waterclefts, spokes or lamellar separations were found in nearly 90% of older humans with vision of 20/30 or better indicating it is possible to start therapy at an early stage of cataract development (13). Until recently a rationale for cataract therapy was unavailable. Presently, two major pathogenetic mechanisms for cataracts may be amenable to therapy: 1) the formation of sorbitol by activation of aldose reductase accelerate cataract development in overt or borderline diabetes (16). This is of significance as 10-15% of senile cataracts occur in patients with abnormal glucose blood levels (4). Inhibition of aldose reductase results in delaying or preventing diabetic cataracts in animals (15, 32). 2) tryptophan plasma levels are increased in both diabetic and non-diabetic humans with senile cataracts (7, 9). Reducing the plasma levels of tryptophan or preventing increased tryptophan penetration into lens may slow down cataract formation. Among pharmacologic agents, aspirin lowers plasma tryptophan by competing at the albumin binding site (26). After dosages of 1800 mg human plasma tryptophan levels are lowered by 50% (26). Furthermore, aspirin increases urinary excretion of tryptophan metabolites such as 30H kynurenine and xanthurenic acid (26). The former metabolite is found in the normal and cataractous lens as well (31).

To determine the effects of aspirin on cataract formation, the prevalence of cataracts was determined in a group of patients with rheumatoid arthritis (RA) alone or affected by diabetes.

Patient population

The medical records of 68 patients with rheumatoid arthritis with or without diabetes mellitus from the Yale-New Haven Hosipital for the period 1975-1979 were reviewed. Intake of aspirin or other medications

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and blood chemistries were obtained. The average aspirin intake (325 mg tablets) was 8.3 tablets with a range of 4-12 tablets taken during 10.4 years (1-42 years) by patients with rheumatoid arthritis and 7.2 tablets with a range 4-12 tablets taken during 8.8 years (3-30 years) by patients with rheumatoid arthritis and diabetes. Of the 19 patients with rheumatoid arthritis and diabetes 12 were diabetics on insulin therapy whereas seven were controlled by diet. Only patients 60 years or older were entered into the study thus excluding all rheumatoid arthritis cataracts, in younger patients, secondary to uveitis or steroid therapy. Of the 68 subjects, four deceased. Eighteen subjects were examined by us and information on all other patients was obtained through local optometrists or ophthalmologists. Entered as cataracts were aphakia of senile lens changes (cortical, nuclear and/or posterior subcapsular) which resulted in best corrected visual acuity of 20/30 or worst. These are the criteria for cataracts used by the FES. No information was obtained from two patients on aspirin and four patients not receiving aspirin.

Statistical analysis – t-tests and analysis of variance among groups were performed to obtain the probability (P) value (11), (28).

Results

The sex and age distribution of patients with rheumatoid arthritis alone or combined to diabetes is shown in Table 1 and 2. The ICD classification of the various subtypes of rheumatoid arthritis syndromes in the aspirin treated and not treated populations are shown in Table 3, and additional medications taken in Table 5. The prevalence of cataracts or clear lenses in the aspirin treated and not treated populations are shown in Table 4. Cataracts were found in four of 29 patients with rheumatoid arthritis receiv-

Table 1.

	Aspirin		No aspirin	
	Males	Females	Males	Females
RH. Arthritis	7	24	6	12
RH. Arthritis & Diabetes	3	7	2	7
Total	10	31	8	19

Table 2.

		Age (years)		
	Aspirin	60-69	70-79	80-89
RH. Arthritis	yes	13	13	5
	no	6	7	5
RH. Arthritis & Diabetes	yes	4	6	–
	no	2	6	1
Total		25	32	11

Table 3.

RH Arthritis type (Classification according to ICD)

	Aspirin	No aspirin
Rh. Arthritis	30	15
Sjogren's Syndrome	2	1
Osteoarthritis vs. Rh. Arthritis	2	4
Osteoarthritis or Ankylosis spondylitis	4	3
Gouty arthritis	1	3
Inflammatory arthritis	2	1
Total	41	27
Rheumatoid Factor Positive	22	12

Table 4.

Effect of aspirin on prevalence of cataracts in rheumatoid arthritis patients

		No Cataract●	Cataract★
Rh Arthritis	Aspirin	25	4
	No aspirin	8	6
Rh Arthritis & Diabetes	Aspirin	8	2
	No Aspirin	1	8
Total	Aspirin	33	6
	No Aspirin	9	14

★Lens opacities causing decrease in VA of 20/30 or greater.
●No axial lens opacities causing decreased VA of 20/30 or greater.

Table 5.

Additional medications taken

	Diabetes + Rheumatoid Arthritis		Rheumatoid Arthritis	
	No Aspirin n=9	Aspirin n=10	No Aspirin n=18	Aspirin n=31
Naprosyn	1	0	–	3
Motrin (Butazolidine)	2	2	5	4
Indomethacin	0	1	3	5
Colchicine	0	0	1	1
Prednisone	4	7	8	10
Plaquenil (Chloroquine)	1	1	1	2
Penicillamine	0	0	0	1
Gold	0	2	2	5
Digoxin	1	2	5	8

ing aspirin and in six of fourteen patients not receiving aspirin. Differences were highly significant ($P < .0005$). Eight of the nine patients with rheumatoid arthritis and diabetes not receiving aspirin developed cataracts whereas only two of ten patients in the same group receiving aspirin developed cataracts ($P < .0005$).

The prevalance of cataract in our rheumatoid arthritis (RA) population not receiving aspirin is 44% (6 of 14). In the FES the prevalance of persons with cataracts for the 65-74 age group was 13.0% and the 75+ age group was 41.4%. Considering the small differences in distribution between our RA-no aspirin population and the FAS population it would appear RA per se does not affect cataract development. Diabetes +RA however did accelerate cataract formation, 89% in non aspirin takers (8 of 9). This is in agreement with the increased incidence of surgically treatable cataracts or aphakia found in diabetics by Caird et al. (2) and by Hiller and Kahn (19).

Discussion

Aspirin administration to patients with rheumatoid arthritis appears to slow down or delay cataract formation. The aspirin effect results from high dosages administered throughout a period of many years. The effects of aspirin on development of heart attacks or cerebrovascular accidents have been tested in rheumatoid arthritis populations (23). However, patients with rheumatoid arthritis populations (23). However, patients with rheumatoid arthritis represent a select group with a multi-system disorder, specific immunological abnormalities, and receiving other therapeutic agents (25). With regard to our cataract study, steroids received by an equal number of patients in the aspirin takers and non-takers groups are cataractogenic (30). However, other anti-inflammatory agents such as naproxen, ibuprofen, indomethacin, gold, penicillamine or chloroquine are not known to induce lens opacities. In a previous study, an exceptionally low prevalence of patients with rheumatoid arthritis was found among patients undergoing cataracts surgery (6). This was attributed to the high aspirin intake of the rheumatoid patients. Only 0.7% of 982 cataract surgery patients in the 45-79 age had rheumatoid arthritis (6). The prevalence of rheumatoid arthritis in the same age group of a recent survey in Rochester, Minn. is 2.5% (21) and in the U.S.A. 1962 survey 12.5% for women and 5.6% for men (24).

Smith and Lakatos found that 1800 mg of acetyl salicylic acid reduce bound plasma tryptophan by 47% and free plasma tryptophan by 50% (26). The mean aspirin daily dosages of our patients were 2300 mgs and 2700 mgs for the rheumatoid arthritis populations with and without diabetes respectively. Thus aspirin effects on cataracts could have resulted from lowering of plasma tryptophan. 80% or more of plasma tryptophan is albumin bound (26). Aspirin displaces bound tryptophan resulting in metabolism to kynurenine or OH-kynurenine which is rapidly excreted in urine (26). Tryptophan may also be displaced from aqueous humor albumin thus decreasing its penetration into lens. Increased urinary excretion of tryptophan metabolites (kynurenine, OH-kynurenine, xanthurenic acid) and lower plasma levels of kynurenine are consistently found in patients with rheumatoid arthritis receiving aspirin (1, 18, 27, 29).

There is good correlation between diabetic cataract development and glucose levels in plasma. Thus, the reduction of cataract formation in patients with rheumatoid arthritis and diabetes receiving aspirin may have resulted from the hypoglycemic effects of this drug (18, 20, 22). Aspirin stimulates insulin secretion following glucose loads in normal humans and in diabetics (22). In diabetic rats salicylic acid lowers plasma glucose levels by 57.8% in 5 hrs (8). In addition, the hypoglycemic action of insulin may be increased by its suppression of fatty acid release from adipose tissue (12).

The acceleration of senile cataracts in diabetics results from increased glycemia and formation of sorbitol (16). Recently we found that sodium salicylate decreases markedly the formation of sorbitol in rat lenses incubated with high glucose (25.5 mmoles) for 3 days (8). Prevention of lens hydration was found in such lenses. Salicylate and acetyl salicylic acid were also found to inhibit purified lens aldose reductase from calf or rat (10). Because salicylates and other organic anions penetrate readily into aqueous humor and lens (8) it could be assumed that lens levels of salicylate approach peak levels in two hours. Following administration of 1800 mg aspirin plasma levels are 0.6-1.0 mmoles (26). Similar levels in aqueous humor and lens would be inhibit lens aldose reductase by at least 50%.

Other effects of aspirin or salicylates on enzymes or transport mechanisms for tryptophan may account for its effect in the non-diabetic lenses. The role of tryptophan on its metabolites in cataract formation is not clear. Lens browning occurs from lens exposure to tryptophan and ultraviolet light (17). Inhibition of Na^+K^+ ATPase, hydration and decreased potentials are found in lenses exposed to tryptamine (3). Sodium salicylate at 1 mmole concentration prevents the binding of tryptophan or kynurenine to human lens protein. However sodium salicylate does not interfere with active transport of ^3H tryptophan of ^3H kynurenine into the cultured rabbit lens (8).

The present studies justify salicylate therapy in patients with rheumatoid arthritis alone or with diabetes to slow down cataract formation. The aspirin dosages are relatively high but nonetheless effective in preventing visually disabling cataracts. Patients were motivated to continuous aspirin intake primarily by the reduction of the pain and improved joint mobility which resulted from it. Additional retrospective studies in progress indicate salicylates slow down cataract formation in other populations as well (5). A prospective study of aspirin in cataract formation may be initiated in the near future.

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