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Familial Eosinophilia with Cardiac Involvement: A Distinct Subset?

Puthalath Koroth Raghuprasad, Sudhir Amaram

Department of Internal Medicine, Medical Center Hospital, Odessa, Texas, USA
Email: pkrp12@gmail.com

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Abstract

In this paper we present a five-generation kindred with familial eosinophilia, associated with valvular heart disease in one of seven members of the second generation, four of sixteen members of the third generation, four of thirty-one members of the fourth generation, and two of twenty members of the fifth generation; the clinical features of the two members of the first generation are unavailable. Of a total of 48 members, 26 had eosinophilia, with counts ranging from 1761 to 6045 cells/mm^3, with apparent autosomal dominant propagation; this confirms the experience of the authors of previous studies on this condition. Genetic analysis on eight members, which we reported in an earlier paper [1], revealed a pericentric inversion of chromosome 10 in two members. The entity of Familial Eosinophilia has been generally considered benign. However, the clinical presentation of this kindred was unusual in that valvular and endocardial damage, was frequent findings, without apparent involvement of the other organs and tissues. Mitral valve damage leading to both stenosis and regurgitation and requiring mitral valve replacement was noted in the index patient. This unique presentation may suggest that in patients with mitral valve disease, if blood eosinophilia is noted, it could point to a non-rheumatic etiology, thus a possible opportunity for treatment to prevent further damage to the heart. This recommendation may be even more timely, as many effective treatments are now available to treat even high-grade hypereosinophilia.

Keywords

Familial Eosinophilia, Autosomal Dominant Propagation, High-Grade Hypereosinophilia

1. Introduction

Familial eosinophilia has been recognized from at least 1909 [2], and during the

first half of the twentieth century many more reports on the subject have appeared [3]-[8]. In 1964 Naiman *et al.* reported their findings on a kindred with eosinophilia and reviewed the world literature [7]. The consensus in most of these studies was that the condition was benign, without organ involvement, and essentially without a need for therapy. The notable exceptions are the patient described by Atmar [4], in whom eosinophilic infiltration of the liver was demonstrated, and two siblings reported by Keshavarzian *et al.* [9] with eosinophilic gastroenteritis. In the latter two siblings, however, the extent of eosinophilia in other family members or in other generations is not known. Superficially, the kindred in the present report resemble the families reported in the above studies. Thus, over 50% of the members evaluated in this family have significant eosinophilia, and in many of them the condition had existed for decades. Closer scrutiny of such individuals, however, revealed frequent occurrence of valvular and endomyocardial disease,

The idiopathic hypereosinophilic syndrome [10]-[22] (HES) encompasses a spectrum of disorders with eosinophilia, multiple organ involvements and generally, until recently, an unfavorable prognosis. In decreasing order of frequency, the organs involved in this syndrome are the heart, the nervous system, the lungs, and the reticuloendothelial system (RES). In the heart, mitral regurgitation, congestive heart failure and endomyocardial fibrosis have been identified with almost equal frequencies; isolated mitral stenosis, however, has not been reported in HES. Likewise, familial occurrence of HES has not been described. Eosinophilia secondary to various disease entities has been described: these include allergic diseases, tissue-invading parasitoses, clonal disorders such as systemic mastocytosis, leukemias and lymphomas and other malignancies, and allergic bronchopulmonary mycoses [23] [24] [25] [26] [27].

Our interest in these kindred rested on the following unique features displayed by most of the family members: high-grade peripheral blood eosinophilia was present in over 50% members of each of the four generations, and isolated cardiac involvement, with no apparent involvement of other organ systems. Valvular involvement in most of the patients was in the mitral valve, and significantly, mitral stenosis was more common than regurgitation, and when the family members, including the index patient died, the death was directly related to their cardiac condition. Finally, since eosinophilia can be controlled with several drugs, especially the biologicals, which in recent years have been more and more specific and increasingly more effective, [28]-[34] when mitral valve disease is discovered, it seems reasonable to do an eosinophil count and not simply assume that valvular lesions were due to prior rheumatic fever, and therefore, no specific therapy is available.

2. Study Population

The index patient, V.K., a 55-year-old Caucasian, who had been a resident of West Texas, was referred by his cardiologist for evaluation of eosinophilia. In

1981 he had a mitral valve replacement for severe mitral stenosis, at age 51. Eosinophilia had been documented in this patient since 1955 (at age 25) and this had ranged from 2% to 45%; the highest total eosinophil count (TEC) was 3940/mm^3. In 1981 mitral valve replacement was done for "rheumatic heart disease"; no particulars about the actual valve lesions were available to us. In 1983 a bone marrow examination was reported as showing "mild eosinophilic infiltration without evidence of a clonal disorder". In March 1987 the index patient underwent an endomyocardial biopsy, which showed "endomyocardial fibroelastosis with evidence of eosinophilic infiltration".

Our inquiry indicated a strong family history of eosinophilia, and that prompted a detailed family survey, and it confirmed this impression. (See the family tree in **Figure 1**). All his family members who have been identified as having eosinophilia were contacted with a view to performing more detailed work up for eosinophilia. Of the surviving family members known to have eosinophilia, ten submitted to such evaluation and they form the study population (**Table 1** and **Table 2**).

Each of the ten subjects who volunteered for the study was evaluated using a detailed history and a thorough physical examination. While taking the history, an attempt was made to determine the age at which eosinophilia was noted, of any foreign travel, or parasitic infestations and of evidence of any other underlying condition known to cause eosinophilia. A complete review of the systems was done, with special efforts at identifying any skin, cardiac, reticuloendothelial, pulmonary or neurological system involvements, and a thorough physical examination was performed, again with particular emphasis on the above organ systems. An electrocardiogram was done on all the individuals who were noted to have a murmur or other evidence of cardiac disease. Blood was drawn from all the subjects for CBC, TEC, CMP, RA factor, ANA, hepatitis B surface antibody (HBs AB), and stool examined for ova and parasites. All laboratory tests were performed at the International Clinical Laboratories, 800 Sovereign Row, Dallas, Texas. All individuals also underwent allergy skin prick testing (SPT) for a battery of allergens, comprising all the relevant regional pollens, mold spores, house dust and dust mites, feathers and cat and dog dander. The technique of SPT was as described in [35].

After the current authors' studies were concluded, these kindred were subjected to further studies by investigators at NIH[1]. Their evaluation detected sustained eosinophilia in 19 of the 52 related subjects studied, four of whom were diagnosed with cardiac abnormalities. In the thirty-three unaffected relatives and ten unaffected spouses there were no cardiac or other system abnormalities. Further laboratory evaluation included IL-3, IL-5, granulocyte-macrophage colony-stimulating factor (GMCSF), serology for parasitic helminthic infections, ANA, serum vit B12, immunoglobulin levels, RA factor, HLA analysis and stool for ova and parasites and these tests were negative or in the normal ranges. They then focused their attention on genetic analysis of several members

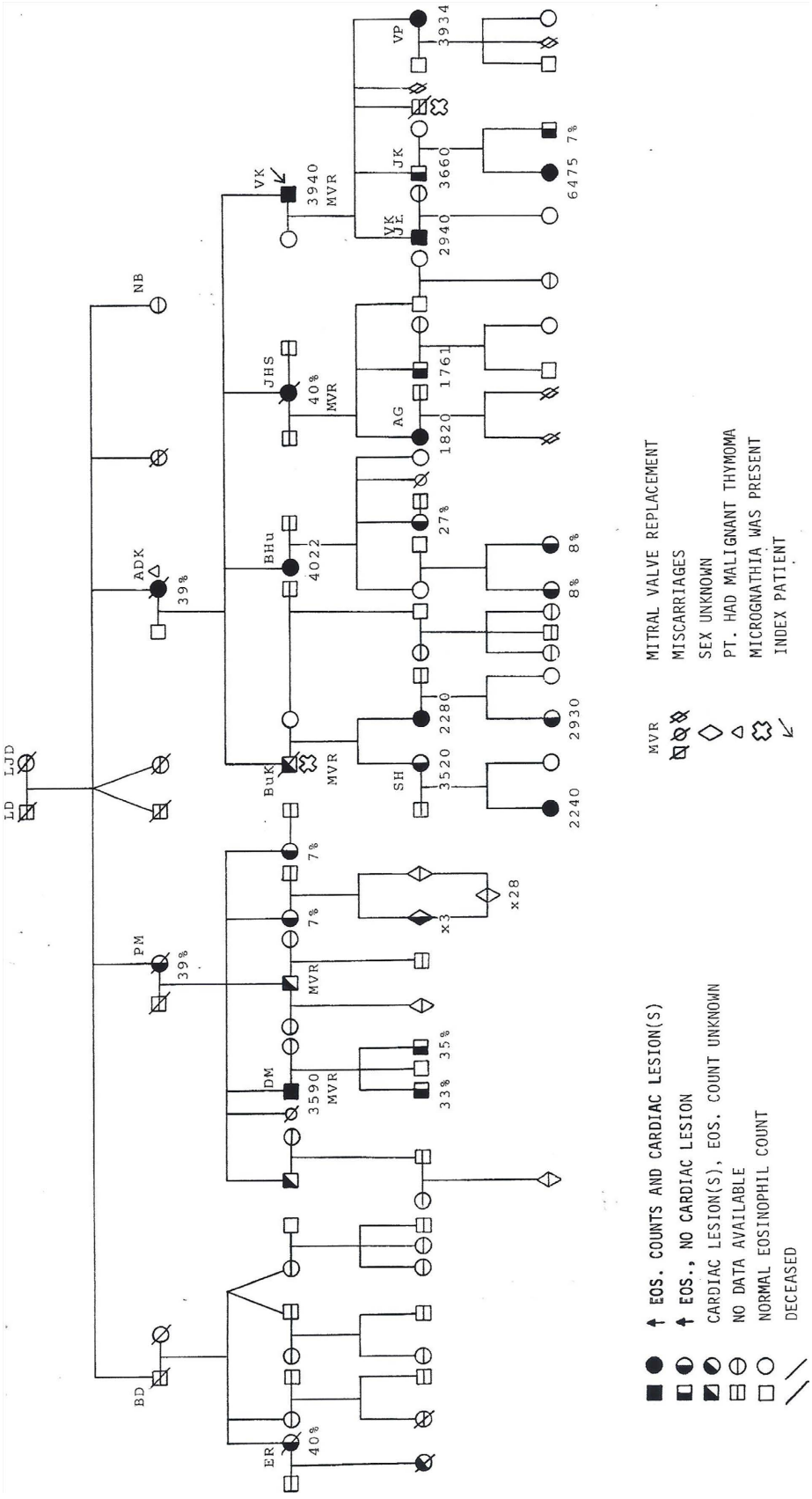

Figure 1. Family tree of the kindred.

Table 1. Clinical features of subjects with eosinophilia.

SUBJ.	AGE	SEX	TEC (mm^3)	HISTORY		PHYS. EXAM	REMARKS
				ALLERGY	OTHER		
V.K.	56	M	3940	None	CHF, MVR/M. Stenosis Cerebral embolus, AF	Loud S1, mid-late diast. Rumble	Index patient, 3rd generation
A.G	40	F	1820	Spring/fall rhinitis Cat, food allergy	Migraine	Nasal congestion, Mid-syst click, murmur Early diast. Rumble	2 miscarriages 4th generation
B.Ho	13	F	2240	None	None	Mid-systolic murmur Aortic area	Discolored teeth 5th generation
B. Hu	62	F	4022	None	HTN, CHF	AF, murmur of AI MI and M. stenosis Liver edge palp.	Sl. Hirsuties 3rd generation
V.P	27	F	3934	Mild all. Rhinitis Cat, horse, food all.	Polycyst. ovary	Soft early syst m or click LSB	1 miscarriage 4th generation
AK	27	F	6475	Mild All. Rhinitis	None	Mid.syst click	5th generation
J.K	36	M	3660	None	Ac. Pancreatitis, Syncopal attacks Lactase def	Liver edge palpable	4th generation
V.K Jr	37	M	2940	Rhinitis	None	Normal	4th generation
J.B	11	F	2930	None	None	Normal	Myopic 5th generation
S.H	34	F	3520	PCN Allergy	None	Nasal congestion	4th generation

TEC = Total eosinophil count; CHF = Congestive heart failure; LSB = Left sternal border; MI= Mitral incompetence; MVR = Mitral valve replacement; AI = Aortic incompetence; AF = Atrial fibrillation; AS = Aortic stenosis.

of these kindred for identifying the mutation (or mutations); after their initial studies were documented in their paper, ongoing efforts were focused on mapping and identifying the genetic mechanisms of the syndrome this family represents.

Figure 1 above shows the family tree of the kindred. (*Since we lost contact with these kindred after the index patient VK died, the above family tree might not have accurate information about any other family members who might have become ill or died since this paper was originally prepared*). Eosinophilia could not be traced proximal to the second generation (BD, PM, ADK, NB), as no records were available pertaining to LD or LJD. Complete blood counts (CBC) with total eosinophil counts (TEC) were done on a total of 48 subjects; eosinophilia was found in 28 of the subjects, possibly suggesting an autosomal dominant disorder. The highest TEC was detected in a granddaughter of the index patient, (TEC 6475/mm^3). The count was over 3000/mm^3 or >30% in 12 individuals, while five more members had counts well over 2000/mm^3 or >20%. It is of interest to note the heavy concentration of positive cases in the immediate family of the index patient, VK; however, we feel that this is an artefact introduced by the vigor with which VK had persuaded his close relatives to obtain

laboratory tests. It is also clear that eosinophila is only found in blood relatives of VK; this perhaps eliminates an environmental factor as possible etiology of eosinophilia in these kindred.

As the study proceeded, it became evident that cardiac disease accompanied eosinophilia in a high proportion of individuals in these kindred. Indeed, our investigative curiosity was first aroused by the loss of two members (SDK and JHS) due to cardiac disease, after initiating this study, but before compliance from even a small number of the family members was forthcoming. These events also aided the study by coaxing many more of the more skeptical members of the kindred to come forward. Even more convincing was the apparent sudden onset of cardiac disease in the only living sibling of the index patient, (BHu), in 1986. She had enjoyed good health until November 1985, but she presented with an abrupt onset of atrial fibrillation, with evidence of involvement of both aortic and mitral valve disease, congestive heart failure and a peripheral eosinophilia of 4022/mm^3. With the addition of her, all siblings of the index patient have or have been known to have cardiac disease, and at least 3 out of 4, also eosinophilia.

Five subjects had symptoms suggestive of allergic rhinitis and/or other allergies. Two of the women had miscarriages. Two subjects had palpable liver but without either symptoms of liver disease or laboratory evidence of it. In some members, the most striking clinical finding was of heart involvement; in all of them a mitral and/or aortic valve disease was noted. Further laboratory data on these individuals are given in Table 2. Serum total IgE ranged from 6 - 39 IU/ml (Normal = 0 - 180). Allergy skin testing to a variety of aeroallergens was positive in two, mildly positive in three and negative in five individuals. Stool examination for ova and parasites and rheumatoid factor were negative in all. Antinuclear antibodies (ANA) were positive in three individuals, with titers varying from 1:80 to 1:320; all had a speckled pattern. White blood counts (WBC) were within normal limits in most, but leukocytosis ranging from 13,000 to 16,800 were seen in three subjects. Red blood cell count (RBC) and platelet counts and RBC indices, and Chemistry profiles were all normal. No immature WBCs were noted in the peripheral blood smear. Some of the specialized tests done on the index patient are indicated in Table 2.

A 12-lead electrocardiogram (ECG) was obtained on all the subjects in the above group with apparent cardiac involvement, and they showed abnormalities in only two, the index patient and his sister BHu; both were the only individuals with symptoms suggestive of cardiac disease. In the index patient, the ECG revealed 1st degree heart block, left anterior hemiblock and intraventricular conduction defect, and in his sister, atrial fibrillation and left ventricular hypertrophy were detected. Echocardiogram was recommended to all individuals with clinical suspicion of heart disease, four obtained it (two of whom had both 2D and doppler ECHOs), and three were abnormal. Aortic and/or mitral valve disease were found in all three. An additional individual obtained echocardiogram at his own initiative, despite lack of clinical evidence of heart involvement (V.K

Table 2. Laboratory/other special test results.

Subj.	Age (Yrs)	Sex	TEC (mm^3)	IgE (IU/ml)	STs*	ECG	ECHOCARD.	ANA (titer)	MISC.
V.K.	56	M	3940	14	Neg	10 HB, I/Vent. Cond. Def	Redu. LV contr. On Doppler	Neg	Endo-myo. Bx + Bone Marrow 10% Eos. Skin and Musc. Bx. Neg
A.G	40	F	1820	32	Neg	N	Aort. Root Dil. AI (Doppler)	1:320 Speckl.	----------
B.Ho	13	F	2240	6	Neg	N	N	Neg	HBs AB +
B.Hu	62	F	4022	62	Neg	AF, LVH	Mild LA Hyper Calc. Mitral & Aortic valve	Pos. 1:80 Speck	Card. Cath: Mild AI LV Dysfunction ESR 44
J.K	36	M	3660	28	Neg	ND	ND	Neg	WBC 16,800
V.P	27	F	2704	172	+++	ND	ND	Neg	----------
A.K	12	F	6475	8	+	ND	ND	Pos. 1:80 Speckl.	WBC 13,500
V.K.Jr	37	M	2940	31	+	ND	AI, Aortic valve Thickened	Neg	----------
J.B	10	F	2930	39	++	ND	ND	Neg	----------
S.H	34	F	3520	ND	Neg	ND	ND	Neg	----------

This table lists the results of the laboratory and other special test results on ten family members with eosinophila, who volunteered to be evaluated.

Results of Stool examination for ova and parasites and Rheumatoid factor are not presented, as they were uniformly negative, when done; all subjects were tested, except for J.K, J.B and S.H stool was not tested.

STs* Allergy skin testing comprised of skin prick testing for the most common aeroallergens in West Texas and Oklahoma TEC Total eosinophil count N Normal ND Not done AI Aortic incompetence (regurgitation).

HBs Ab Hepatitis B surface antibody AS Aortic stenosis LVH Left ventricular hypertrophy.

+++ Strongly positive; ++ moderately positive; + mildly positive.

Jr); this showed aortic insufficiency and valve thickening. The cardiac involvement in the index patient was unique in that, from the beginning he was noted to have mitral stenosis as the isolated lesion. In the index patient and his sister BHu, evidence of reduced LV wall contractility was noted (Table 2).

The index patient's cardiac status was studied in greater detail after he experienced increasing dyspnea on exertion. Electrocardiogram showed 1st degree heart block, and intraventricular conduction defect and a doppler echocardiography showed reduced left ventricular contractility; coronary angiography revealed reduced ejection fraction. These were followed by an endomyocardial biopsy, which showed infiltration by eosinophils and endocardial fibroelastosis. The salient findings of these and also the autopsy findings of this patient's heart were presented in our earlier paper [1].

In March 1987, the index patient became aware of deterioration in his exercise tolerance, and the work up showed ejection fraction of 15% - 20% and diffuse hypokinesis of the left ventricular wall. Shortly thereafter the patient expired. An

endomyocardial biopsy at autopsy, reported in our paper [1], showed "endocardial fibroelastosis, which, by trichrome staining showed marked increase in elastic and fibrous tissues extending into the myocardium".

3. Discussion

The most striking feature of this five-generation kindred is, of course, the high-grade peripheral eosinophilia in each generation, implying an autosomal dominant pattern of inheritance. Thus, this kindred fits the syndrome described by Gaugain in 1909 [2] and further defined by others during the ensuing decades [3] [4] [5] [6] [7] variously as "Familial", "constitutional" or "hereditary" eosinophilia. However, all prior descriptions of this syndrome stressed the absence of serious adverse organ systems dysfunction. In the kindred described in this paper, of 48 family members, 26 individuals had high-grade eosinophilia (54% of family members), and mitral or aortic valve lesions were present in members from each generation. This study as well as the study reported by Lin *et al.* [1] have ruled out any of the secondary conditions that could account for the eosinophilia in this kindred. The syndrome of Idiopathic Hypereosinophilic syndrome is not known to have familial transmission, and by definition multiple organ systems are involved. Thus, the condition described in this paper is not even a subset of the hypereosinophilic syndrome. However, familial eosinophilia with cardiac involvement as s subset is a plausible classification.

Two observations in the cardiac involvement in these kindred deserve special mention. First, at least in one individual in the kindred (VK), the earliest or primary involvement in the heart was isolated mitral stenosis, and mitral stenosis was present in addition to mitral regurgitation, and aortic valve disease in another member (BK). This has not so far been reported in HES or other conditions with eosinophila. If this observation is borne out by other studies of eosinophilic conditions, eosinophilia may have to be included in the causes of mitral stenosis. The second observation is that, even in those individuals without mitral stenosis, the valvular damage was always left-sided; mitral or aortic valve thickening or regurgitation were mostly observed. This latter observation is, of course, identical to prior reports on HES [11] [12], and it begs the question, why? We are tempted to speculate that this effect is due to disruption of the granules of the large numbers of circulating eosinophils, and in the heart, such disruption occurs more readily in the higher pressure left-sided heart chambers. A logical comparison can be made with the localization of cardiac lesions in carcinoid syndrome with hepatic involvement occurring in the right heart chambers. Experiments can be designed to test this hypothesis. For example, differential measurements of the major basic protein or cationic protein (two of the common eosinophilic granules) in the venous versus the arterial blood or right and left heart blood should show higher amounts of those in the left heart, if the above speculation is accurate. Of course, like all high-grade eosinophilic conditions, in these kindred also, endomyocardial damage from eosinophilic infiltra-

tion is observed when biopsy of the heart was done, as in the index patient.

Certain clinical associations we found in these kindred are unexplained at present. Miscarriages in two subjects with high eosinophil counts (AG and VP), micrognathia in two others (See **Figure 1**) are two of the features currently under investigation. Chromosome analysis at NIH detected "a pericentric inversion of Chromosome 10, in [10] (p11.2q21.2) and this has been reported in [1]. Positive ANA in low titers in three individuals is also not explained at present; this might be of no significance, unless the titers increase later in life. No other immunological features has appeared in any member of this kindred.

Our experience with these kindred having an autosomal dominant disorder, with high penetrance and high incidence of cardiac involvement, resulting in significant symptomatic damage and even death due to the cardiac disease, makes us wonder if "masterly inactivity" is the right course of action. This is especially relevant, as the cardiac damage, once incurred, is irreversible. On the other hand, since several treatment modalities have become available to treat eosinophilic conditions, by specifically targeting the eosinophil at various stages of its development [29]-[34] it seems obligatory for the clinicians to treat the eosinophilia, ideally before cardiac damage sets in and even to reduce further damage, if such damage had already occurred at clinical presentation. We believe the risk benefit ratio of treatment of eosinophilia is quite acceptable in these kindred, although such an action constitutes "prophylaxis" of cardiac damage.

4. Conclusion

These kindred, with high-grade eosinophilia in four generations, seem to manifest features of "familial eosinophilia" and of the "hypereosinophilic syndrome (HES)". However, the absence of involvement of organ-systems other than the heart in most subjects argues against HES; a subset of familial eosinophilia with isolated cardiac damage could be considered. Since mitral valve disease is prominent in the cardiac involvement in these kindred with heart disease, it seems reasonable to recommend checking for eosinophilia in all patients with valvular heart disease, especially, of the mitral valve, and not simply attribute the cardiac disease to rheumatic fever. This is especially important as there are several treatment modalities available to us now to control eosinophilia, prominent among which are the biologicals. Such a pro-active approach might prevent the ravages of hypereosinophilia these kindred suffered, including the valvular heart surgery and indeed the high rate of death from cardiac disease in some.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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