APOE gene polymorphisms and diabetic peripheral neuropathy

Christodoulos Monastiriotis[1], Nikolaos Papanas[1], Stavroula Veletza[2], Efstratios Maltezos[1]

[1]Outpatient Clinic of the Diabetic Foot, Second Department of Internal Medicine, Democritus University of Thrace, Greece
[2]Laboratory of Medical Biology, Medical School, Democritus University of Thrace, Greece

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Corresponding author:
Dr. Christodoulos Monastiriotis
Limnou 7
Alexandroupolis 68100
Greece
Fax: +30 25510 74723
E-mail:
c_monastiriotis@yahoo.com

Abstract

Genetic factors may influence the natural course of diabetic peripheral neuropathy and explain some of its variability. The aim of this review was to examine the association between apolipoprotein E (apoE) gene polymorphisms and diabetic peripheral neuropathy. Four relevant studies were identified. The two earlier works provided evidence that the ε4 allele is a risk factor for this complication, while the two more recent studies were negative. Important differences in the methodology used and in the populations included are obvious, rendering difficult the comparison between studies. In conclusion, the association between APOE gene polymorphisms and diabetic peripheral neuropathy is still unclear. Available evidence is rather limited and results have so far been contradictory. Future studies should employ more robust methodology, adjusting for potential confounders and for the prevalence of neuropathy in the general population with diabetes.

Key words: apolipoprotein E, diabetes mellitus, diabetic neuropathy, polymorphisms.

Introduction

Diabetic neuropathy is a chronic microvascular complication of diabetes mellitus (DM). It is a heterogeneous group of disorders, whose pathophysiology is extremely complex and which affects both the somatic and the autonomic component of the peripheral nervous system [1-6]. Distal symmetric polyneuropathy, also called peripheral neuropathy, is the most common form of this complication, affecting about 30% of patients with DM [1, 2, 4]. It has also been noted that some patients show minor or no clinical signs of neuropathy even after many years of diabetes, while others suffer from severe neuropathy by the time of, or before, the diagnosis of DM [7-10]. There is now ample evidence to support the view that pathogenesis starts even before the diagnosis of overt DM, during the so-called pre-diabetic stage [7].

Several factors have been identified to affect the course of diabetic peripheral neuropathy [1-6] (Table I). Diabetes duration and degree of glycaemic control are the major factors affecting incidence and severity, while patient age and height, hypertension and dyslipidaemia are other contributory factors [2, 5-7]. Nevertheless, even within comparable DM duration and glycaemic control, there is a considerable degree of between-patient variability in terms of clinical manifestations and severity of diabetic peripheral neuropathy [2, 5-7]. In view of this variability, it has been hypoth-

Table I. Factors that affect the course of diabetic peripheral neuropathy (based on references [1-6])

Diabetes duration
Poor glycaemic control
Height
Hypertension
Age
Visceral obesity
Smoking
Hypoinsulinaemia
Dyslipidaemia
Genetic factors

esised that genetic factors may influence the natural course of diabetic peripheral neuropathy.

In recent years, genetic factors have attracted considerable interest thanks to the evolution of molecular biology [11-15]. Indeed, it has now become much easier to investigate the potential correlations between gene polymorphisms and the course of diabetic complications, including neuropathy. Thus far, several gene polymorphisms have been studied [11-15]. These include genes encoding peptides that play a key role in the metabolic or immunological pathways implicated in disease pathogenesis [11-15]. Aldose reductase [11], α-2B adrenoreceptor [12], Na/K ATPase [13], capsaicin receptors [14], and metabotropic glutamate receptors [15] are only some of the polymorphic gene products previously studied in relation to diabetic neuropathy.

Among these investigations, apolipoprotein E (usually abbreviated as apoE for the protein, and APOE for the gene) gene polymorphisms are of particular interest. Apolipoprotein E seems to be of paramount importance in ameliorating oxidative stress and reducing inflammation [16]. It is the major apolipoprotein encountered in the central nervous system (CNS) [17]. It is also found in the peripheral nervous system, where it is produced by non-myelinated Schwann cells, ganglionic satellite cells and macrophages [18]. A correlation has already been shown between APOE gene polymorphisms and the severity of several CNS degenerative diseases [19]. Moreover, the relation of APOE polymorphisms to the severity of Alzheimer's disease is now well established [20-23]. Studies are also being conducted to ascertain the association between APOE gene polymorphisms and peripheral neuropathies, especially diabetic peripheral neuropathy.

The aim of the present review was to provide an outlook on the association between APOE gene polymorphisms and diabetic peripheral neuropathy.

Search strategy

The electronic search was based on the PubMed, Embase and Google Scholar databases up to June 2012 using combinations of the following keywords: complications, diabetes, gene, neuropathy, pathogenesis, peripheral neuropathy, polymorphism, APOE. All types of articles written in English were included, while works written in other languages were only studied in abstract form.

Evidence for the association between APOE gene polymorphism and diabetic neuropathy

Studies investigating the association between APOE gene polymorphisms and diabetic neuropathy are summarised in Table II.

The first study was carried out in Japan by Tsuzuki and colleagues and published in 1998 [24]. It included 158 patients with type 2 DM, who were examined for diabetic retinopathy, nephropathy and neuropathy. Severity of neuropathy was assessed by a scale devised by the authors. All patients were APOE genotyped and divided into three genotype groups: E2 (genotypes ε2/ε2 and ε2/ε3), E3 (genotype ε3/ε3) and E4 (genotypes ε3/ε4 and ε4/ε4) [24]. The three groups did not differ in terms of patient age, diabetes duration, body mass index or glycated haemoglobin (HbA_{1c}). No significant differences were observed in the rates of retinopathy and nephropathy among the three groups. However, neuropathy was significantly ($p < 0.05$) more frequent in the E4 group (39%), compared to the E3 group (28%) and the E2 group (23%). Furthermore, patients in the E4 group presented earlier and more severe neuropathy than those in the other two groups [24]. The limitations of this study include the small patient series and the subjective evaluation of neuropathy severity using a non-standardised scale. Nonetheless, the results concur with those of current evidence on the association of APOE polymorphisms with the severity of CNS diseases [21, 25-27], inasmuch as the ε4 allele was related to more severe disease.

Two years later, Bedlack *et al.* [19] published a literature review on the relation between APOE gene polymorphisms and several neuromuscular diseases. Among other things, they discussed diabetic peripheral neuropathy, reviewing the previous study, which was then the only available work. In 2003, these authors reported on their own findings in this area [28]. They included 187 patients with DM, divided into two groups: the group of ε4/ε4 or ε3/ε4 genotypes and the group comprising other genotypes (including patients with ε2/ε3, ε3/ε3 and ε2/ε4). Severity of neuropathy was evaluated by the NIS-LL (Neuropathy Impairment Score in the Lower Limbs) [29] scoring system. Comparison

between groups was carried out by multiple regression analysis with adjustment for age, DM duration, as well as most recent and the higher detected triglyceride and HbA_{1c} levels. Patients in the ε3/ε4 or ε4/ε4 group exhibited more severe neuropathy, similar to that associated either with an additional 15 years of age or with an additional 15 years of diabetes duration [28]. Of note, glycaemic control or triglyceride levels were not significant predictors in this model.

Surprisingly, in 2005 two new studies questioned the correlation of APOE gene polymorphisms with severity of diabetic neuropathy. The first work included 56 patients with clinically overt neuropathy [30]. These underwent an oral glucose tolerance test and were divided into three groups: patients with normal oral glucose tolerance test, those with impaired glucose tolerance and those with DM. Genotyping for the APOE gene was carried out using skin biopsy specimens and the severity of neuropathy was evaluated using the Neuropathy Impairment Score (NIS) [31]. According to their genotype, patients were divided into APOEε4(+) and APOEε4(–). The ε4 allele rate among subjects with DM or impaired glucose tolerance was not significantly different from that of the general population in the United States and Europe, as based on previous prevalence studies. The authors concluded that the ε4 allele was not a risk factor for neuropathy [30]. The limitations of the study include the small patient series, the unidentified cause of neuropathy among subjects with normal oral glucose tolerance test and the use of NIS, which may be criticised as not very sensitive for small fibre dysfunction.

In the same year, another study was published by Voron'ko *et al.* [32] in Russia including 180 patients with type 1 DM. According to the presence or otherwise of neuropathy, patients were divided into two groups: those with shorter than 5 years DM duration who exhibited clinical neuropathy, and those with longer than 10 years DM duration who had no clinically manifest neuropathy. Neuropathy was diagnosed according to the San Antonio consensus on the diagnosis of neuropathy [33] and the Neurodiab Subcommittee criteria [34]. Genotype rates and allele rates were measured in each group and no significant differences were observed [32]. Thus, it was concluded that APOE gene polymorphisms did not affect the severity of diabetic neuropathy. The limitation of this study is the use of a unique division of patients according to the severity of neuropathy without adjustment for covariates (such as age, gender, DM duration, level of glycaemic control). As a result, it may be argued that the two patient groups might be essentially different and incomparable, diminishing the clinical implications of the results.

Table II. Studies examining the association of APOE gene polymorphisms with diabetic peripheral neuropathy

Authors (publication year)	Population studied	Number of patients	Neuropathy scale	Groups compared	Results	Conclusions
Tsuzuki *et al.* (1998) [24]	Japanese patients with type 2 diabetes	158	Devised by the authors	E2 (ε2/ε2 and ε2/ε3) vs. E3 (ε3/ε3) vs. E4 (ε3/ε4 and ε4/ε4)	Higher frequency of diabetic neuropathy in E4 (39%) than E3 (28%) and E2 (23%) ($p < 0.05$)	ε4 is a risk factor for diabetic peripheral neuropathy
Bedlack *et al.* (2003) [28]	American patients with type 1 and type 2 diabetes	187	NISLL	Group A: E3/4 and E4/4 vs. group B: other alleles	Group A: averaged 3.12 NISLL points more than group B ($p = 0.02$)	ε4 is a risk factor for diabetic peripheral neuropathy
Zhou *et al.* (2005) [30]	American patients with peripheral neuropathy	56	NIS	Normal OGTT vs. IGT vs. diabetes mellitus	APOE status did not predict NIS ($p = 0.88$)	ε4 is not a risk factor for diabetic peripheral neuropathy
Voron'ko*et al.* (2005) [32]	Russian patients with type 1 diabetes	180	Devised by the authors	Group A: diabetes duration ≤ 5 years and peripheral neuropathy vs. group B: diabetes duration > 10 years without peripheral neuropathy	No significant differences of genotype or allele frequencies observed between the two groups ($p < 0.881$)	ε4 is not a risk factor for diabetic peripheral neuropathy

NIS – Neuropathy Impairment Score, NIS-LL – Neuropathy Impairment Score in the Lower Limbs, OGTT – Oral Glucose Tolerance Test, IGT – impaired glucose tolerance

Discussion

The present review examined the evidence for the association between APOE gene polymorphism and diabetic peripheral neuropathy. This potential relationship is of importance, given the data on some contribution of apoE isoforms to nerve repair and regeneration. First, experimental research has shown that traumatic or toxic sciatic nerve injury leads to increased synthesis of apoE by Schwann cells [35, 36]. Interestingly, apoE deficient mice fail to accomplish complete nerve regeneration after sciatic nerve injury. Indeed, regeneration looks morphologically normal on light microscopy [37], but electron microscopy reveals fewer and abnormally shaped small, unmyelinated axons, compared with wild-type animals [38]. Secondly, human studies have provided evidence that the APOE4 allele confers increased risk of developing early Alzheimer's disease [22], while the APOE2 allele lowers this risk [23]. Furthermore, the APOE4 allele is related to worse outcome after intracranial haemorrhage [25] or head injury [26], as well as to increased likelihood of cognitive impairment following cardiopulmonary bypass surgery [39, 40]. In addition, some recent lines of evidence suggest that APOE gene polymorphisms are associated with lipid profile, thereby affecting cardiovascular risk and longevity as well [41].

The evidence on the association between APOE gene polymorphism and diabetic neuropathy is still rather limited and definitive conclusions cannot be drawn [24, 28, 30, 32]. This uncertainty is further enhanced by the important methodological differences between the studies. Indeed, different scoring systems for the severity of diabetic peripheral neuropathy, different genotype group formation, and discrepancies of populations studied (e.g. type 1 only or both types of diabetes) become immediately clear [24, 28, 30, 32]. Consequently, it is extremely difficult to compare studies with each other, and still less to attempt a pooled data analysis.

A further important issue to consider is the differences in the general populations from which patient series were drawn. Essentially, the different conclusions on the role of APOE gene polymorphisms in diabetic neuropathy may largely be, beyond the aforementioned differences in methodology, due to the fact that the studies were carried out in populations of different origin [24, 28, 30, 32]. Accordingly, it is conceivable that the role of apoE in the pathogenesis of diabetic peripheral neuropathy is enhanced or diminished by other uncontrolled genetic factor(s) that are differently distributed among various populations, thereby altering the association of APOE gene polymorphisms with diabetic peripheral neuropathy. Of note, only Zhou *et al.* [30] compared allele rates between the patients studied and the general population, attempting to ensure generalisability of their findings.

Hence, additional enquiries are required to clarify the association between the APOE gene polymorphisms and diabetic peripheral neuropathy. It would be useful to carry out studies in different populations using the same method [42]. Ideally, studies should employ a common scale to quantify the severity of neuropathy, common genotype group division and comparison to the genotypic rates of the general populations to ensure that patient series included are representative of the background populations. In this fashion, it would be possible to attempt a meta-analysis of results and clarify the potential role of APOE gene polymorphisms in the pathogenesis and natural course of diabetic peripheral neuropathy.

Conclusions

The association between APOE gene polymorphisms and diabetic peripheral neuropathy remains unclear at the moment. Available evidence is rather limited and results have thus far been contradictory [24, 28, 30, 32]. Important discrepancies may be indentified in methodology and in populations used. Thus, additional research is required to elucidate the potential role of APOE gene polymorphisms in the pathogenesis and natural course of diabetic neuropathy. Future studies should employ more robust and reproducible methodology [42-45], but also adjust for potential confounders, as well as for the prevalence of neuropathy in the general diabetic population. Such works will be very useful, contributing to the accumulating knowledge on the various novel and, at times, paradoxical issue of diabetes [46]. It is anticipated that they will enrich our knowledge on the causal pathways of diabetic neuropathy.

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