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RETINAL FUNCTIONS MODIFICATIONS AS REFLECTED ON THE ELECTRORETINOGRAM IN DIFFERENT STAGES OF DIABETIC RETINOPATHY

THESIS

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Contents

INTRODUCTION

Diabetes mellitus is one of the commonest metabolic disorders influencing the retina which when causing retinopathy, becomes one of the most challenging problems facing ophthalmologists. Today diabetic retinopathy including maculopathy is considered as one of the commonest causes of blindness in industrial countries (Bodonowitz and Kroll, 1996).

In the retina the primary site of the damaging effect of diabetes has been located either in the inner retinal layers (i.e., bipolar, ganglion, inner plexiform, and amacrine cells (Bresnick and Palta, 1987), or alternatively in the outer retinal layers (i.e., photoreceptors or retinal pigment epithelium (Esner et al., 1987).

Eyes with diabetic retinopathy show electrophysiological abnormalities, the severity of which correlates to a substantial degree with the extent of retinal vascular affection (Bresnick et al., 1984).

The electroretinography records the graded electrical response generated at the outer layers of the retina, representing the functional state of those layers up to the ganglion cell layer (Henkes, 1981).

Recent studies have shown that functional abnormalities may precede ophthalmoscopic evidence of retinal disease (Cathelineau and Cathelineau, 1991). Electrodiagnostic procedures may be also valuable in identifying patients at risk of developing proliferative diabetic retinopathy and may have prognostic usefulness in the assessment of retinal function in diabetic eyes with opaque media e.g. cataract or vitreous haemorrhage thus helping the selection of suitable candidates for surgery (Biersdorf, 1984).

Nowadays clinical electrophysiology has become an indispensable method for studying retinal diseases and exploring retinal function.

AIM OF THE WORK

The aim of this work is to study the retinal function as reflected on the electroretinographic changes in different stages of diabetic retinopathy. And to try to find out a relationship between visual acuity, fundus changes as documented by fluorescin angiography on one hand and electrical activity of the retina on the other hand.

This work may be used to find out if ERG changes can be a good indicator for the objective evaluation of the severity of diabetic retinopathy.

REVIEW OF LITERATURE

DIABETIC RETINOPATHY

Diabetic retinopathy is generally considered to be a vascular disease causing loss of vision by macular oedema, vitreous hemorrhage or retinal detachment. However it may also be a neurosensory disorder, with functional changes occurring before microvascular abnormalities (Cathelineau and Cathelineau, 1991).

Epidemiology:

Studies of the epidemiology of a disease are important for establishing hypotheses of its pathogenesis. Epidemiological studies showed a strong relationship between glycaemia and diabetic complications, in both type I and type II diabetes there is a continuous relationship between prevailing glycaemia and risk of progression of complications (Skyler, 1996).

Other factors have been described as having effects on the development and progression of diabetic retinopathy e.g. puberty. However the mechanism by which puberty might exert its effect on the development of early retinopathy is unknown although hormonal factors were postulated (Knowles et al., 1965).

Several reports suggested that progression of diabetic retinopathy is directly related to the systolic blood pressure, and to a lesser extent to diastolic blood pressure (Bellini et al., 1995).

Rand et al. (1985) found a strong association between proliferative retinopathy and the presence of HLA-DR phenotypes 4/0, 3/0 and x/x. Other ocular factors may influence the prevalence and severely of diabetic retinopathy

such as glaucoma, which was reported to reduce both the prevalence and severity of diabetic retinopathy in affected eyes (Becker, 1967). Myopia was also found to decrease both prevalence and severity of diabetic retinopathy (Rand et al., 1985). Posterior vitreous detachment may prevent the progression of diabetic retinopathy because of the missing scaffold for forward new vessels growth (Hamilton et al., 1996). Removal of cataract even with a small incision may aggravate both existing macular oedema and proliferative diabetic retinopathy (Hamilton et al., 1996).

Pathogenesis of diabetic retinopathy:

It is presumed that the initial pathological changes which occur in the small vessels of the diabetic retina include endothelial cell and pericyte damage, which can be demonstrated by trypsin digest techniques (Engerman et al., 1971). The break down of the blood-retinal barrier may occur early in the caurse of diabetes, before retinopathy is observed clinically (Cuhna et al., 1975).Thickening of the basement membranes, "swiss cheese"-like vaculization and deposition of fibrillar collagen in the midest of the usual homogeneous pattern of basement membranes collagen have been widely observed (Rand et al., 1985). Recently, an experimental study showed the presence of microaneurysms, acellular capillaries, or pericyte ghosts in small retinal vessels at a very early stage of retinopathy (Danis, 1993).

Over the past few years, the neuroophthalmologic use of clinical electrophysiology seems to have somehow modified the view that the initial insult to the diabetic retina is a microangiopathy.

Cathelineau and Cathelineau (1991), suggested the occurrence of an early neurosensory disorders in the diabetic retina. However, not all investigators have

found functional changes before the appearance of vasculopathy in the diabetic retina (Nesher and Trick, 1991).

Classification of diabetic retinopathy according to Early Treatment Diabetic Retinopathy Study (ETDRS), 1991:

1-Non-proliferative diabetic retinopathy (NPDR) :

a- Mild.

b- Moderate.

c- Severe.

2-Proliferative diabetic retinopathy (PDR):

a- Early PDR.

b- PDR with high risk criteria.

c- PDR including advanced diabetic eye disease (vitreous haemorrhage and tractional retinal detachment).

3-Diabetic maculopathy

- Macular oedema
- Clinically significant macular oedema(CSMO)

Mild non-proliferative diabetic retinopathy:

The earliest sign to appear in mild non-proliferative diabetic retinopathy is the microaneurysms. The location of which indicates areas of capillary closure (Bresnick, 1990). Microaneurysms appear to drive from retinal capillaries and

are usually found in the vicinity of occluded capillaries. Microaneurysms can occur at any level between the superficial and deeper retinal capillary networks or even from the choroidal circulation (Kohner et al., 1986).

Moderate and severe non-proliferative diabetic retinopathy:

Intraretinal haemorrhages may appear secondary to rupture of microaneurysms, capillaries or venules. Dot haemorrhages with very distinct borders, and blot haemorrhages with somewhat fuzzier borders, are located deeper within the outer plexiform and inner nuclear layers. Dot and blot haemorrhage are the result of haemorrhagic retinal infarcts which are caused by arteriolar occlusion with later reperfusion of the arteriols (Bresnick, 1990).

Flame shaped haemorrhages occur in the superficial nerve fiber layer, here the tight organization of the cells and the relative paucity of extracellular space allow the hemorrhages to follow the configuration of nerve fibers or axons (Olk and Lee, 1994). More advanced non-proliferative retinopathy due to extensive arteriolar closure is clinically manifest in cotton wool spots which are small infarcts of the nerve fiber layers.

Fluorescein angiography shows early blockage of fluorescein by the cotton wool spots or dark blot hemorrhage and associated with zones of capillary non perfusion surrounding an occluded terminal arteriole (Kohner and Henkind, 1970).Venous beeding represents focal area of venous dilatation with apparent thinning of venous wall, in addition there may be venous sheathing and focal narrowing. These changes are associated with capillary non perfusion and retinal ischaemia and are definitely correlated with an increased probability of progression to proliferative retinopathy (Early Treatment Diabetic Retinopathy Study Group report number 12,1991).Intraretinal microvascular abnormalities

(IRMA) refers specifically to the dilated tortuous telangiectatic channels between diseased arterioles and venules which may represent intraretinal neovascularisation (Muraoka and Shimizu, 1984), or dilatation of preexisting channels, or "shunt vessels" (Cogan and Kuwabare, 1963).

Criteria of severe non-proliferative retinopathy according to early treatment diabetic retinopathy study research group report No 7 (1991) are one of the following :

1-Severe intraretinal haemorrhages in four quadrants.

2-Venous beeding in two quadrants.

3-Moderately severe IRMA in one quadrant.

Proliferative diabetic retinopathy:

The hallmark of proliferative diabetic retinopathy is neovascularization, these neovessels either arise from the optic disc (neovascularization at the disc "NVD") or elsewhere (neovascularization elsewhere "NVE") and proliferate along the retinal surface or into the vitreous with or without a fibrous components (Davis, 1989). Many theories have been postulated about the etiology and pathogenesis of development of these new vessels. Most observers agree that ischaemia of the inner retinal layers secondary to closure of parts of the retinal capillary bed will result in dilatation of other parts of the vascular bed (Patz, 1982). While other investigators suggest that vasodilatation itself will stimulate endothelial proliferation and new vessel formation (Wolbarsht et al., 1980). Others have suggested that vasoproliferative growth factors of unknown origin are produced, acting locally and diffusing through the vitreous to other areas of the retina, to the optic disc and into the anterior chamber where it is