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Electroretinographic Findings of Patients with Long Duration Diabetes but No Retinopathy: A Pilot Study Using a Handheld RETeval-DR™ Device

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ABSTRACT

Aims/hypothesis: Diabetic retinopathy is usually considered as a microvascular disease, but neurophysiological abnormalities of the retina occur early and have been postulated to play a role in the pathogenesis of diabetic retinopathy. However, a causal relationship has not been established. Hitherto, specialized equipment and facilities have been required for studying this aspect of retinal changes in diabetes. Recent advances in technology enabled use of a handheld RETeval-DR™ device to perform electroretinography on patients with a long duration of diabetes (>15 years) but no diabetic retinopathy. The aim is to determine whether in this specific clinical setting "normal retinal microvascular morphology" is also characterised by "normal retinal electrophysiology".

Methods: Full-field electroretinography was performed with a handheld RETeval-DR™ device which generates results on Implicit Time and Amplitude, representing respectively the speed and the magnitude of electrical activity of the retinal cells in response to the flickering flashes of light. Altogether 35 diabetic patients (n = 26 type 2 and n = 9 type 1) with diabetes > 15 years, but no or only very minimal retinopathy, were tested (Retinopathy –ve Cohort). Non-diabetic participants (n=25) were also studied as Normal Controls. Additionally, their electrophysiological results were compared with data extracted from 9 diabetic patients who have long duration of diabetes and retinopathy, but without previous laser treatment (Retinopathy +ve Controls).

Results: The Implicit Time of the Retinopathy –ve Cohort was only minimally longer than Normal Controls (30.5 ± 1.8 vs 29.4 ± 1.2 msec), but the Amplitude was significantly reduced by about 30% (23.2 ± 5.3 vs 31.8 ± 9.4 uv, $p<0.01$). The Amplitude of the Retinopathy -ve Cohort was lower than the Retinopathy +ve Controls (Amplitude 28.9 ± 7.8 uv), despite the latter group being affected by retinopathy.

Conclusions/Interpretation: In this pilot study, we found the eyes of patients with longstanding diabetes but without retinopathy have significantly abnormal retinal electrical activity. Thus, retinal electrophysiological changes are not direct correlates of the propensity to develop diabetic retinopathy.

INTRODUCTION

Diabetic retinopathy increases with duration of diabetes and hyperglycaemia, but the presence of retinopathy in individual patients is unpredictable. The basis for this

difference in susceptibility is not clear and understanding this phenomenon would be of great importance in developing strategies for prevention of this diabetes complication. Diabetic retinopathy is usually considered a microvascular disease and most of the research efforts have been directed towards the microvasculature. However, 95% of the retina is actually composed of neural tissues and their abnormalities, either alone or as part of the retinal neurovascular unit, have been postulated to play a role in the development of retinopathy [1,2]. To provide support for this hypothesis, clinical trials such as the European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR) has been designed to test whether diabetic retinopathy can be ameliorated by pharmacological treatment with neuro-protective agents [2]. At a more fundamental level, documentation of neurophysiological abnormalities by electroretinography and correlation with clinical status could provide important information [3-7]. Hitherto, performance of electroretinography has required rather sophisticated equipment and facilities and/or slightly invasive methods (eg: placement of recording electrodes on the cornea). The commercial availability of the handheld RETeval-DR™ device has simplified this procedure [8,9]. Although the RETeval-DR™ is primarily marketed as a device used for screening diabetic retinopathy in clinical settings, its utility has allowed us to conduct research on the possible relationship between retinal neurophysiological changes and diabetic retinopathy.

In this pilot study, we performed electroretinography on patients with a long duration of diabetes (> 15 years) sufficient for retinopathy to emerge and yet have no, or very minimal, diabetic retinopathy. The aim is to determine whether, in this specific clinical setting, "normal retinal microvascular morphology" is also characterized by "normal retinal electrophysiology". The findings could have important implications on the pathogenesis of diabetic retinopathy.

METHODS

Full-field electroretinography was performed with a handheld RETeval-DR™ device (Figure 1) according to the technique described in details by Maas et al., [8]. This device emits flickering lights at 30Hz to stimulate retinal electrical activity which is recorded by skin electrodes placed below the lower eyelids (Figure 1). The RETeval-DR™ device generates results on Amplitude (uV), which is the magnitude of electrical response and Implicit Time (msec), which is the time elapsed between stimulation and the point of maximal amplitude (wave's peak). Thus, a low number indicates faster neurovascular transmission. In traditional ERG, many components of the retinal electrical activities can be separately analysed but for RETeval-DR™ this is not possible. Pupil Diameter (mm) response to different intensity of the flickering light is also automatically monitored during the test to adjust for the intensity of light reaching the retina. Apart from providing these three parameters individually, a composite score derived from them is calculated automatically by the RETeval-DR™ device. A typical printout is shown in (Figure1). A score < 20 indicates that the risk of vision threatening retinopathy is < 1%. Only data for the right eye stimulated by light strength of 16 Troland units are presented in this paper, but they are representative of the overall results.

The Retinopathy –ve Cohort was selected from those attending the Diabetes Centre of the Royal Prince Alfred Hospital who fulfilled the inclusion criteria. That is, type 1 or type 2 diabetes, with a duration of diabetes > 15 years and no, or only minimal diabetic retinopathy detected during their routine clinical assessment. Retinopathy status was documented by either direct examination or retinal photography within the previous 12 months and classified according to the International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales [10]. This classification is based on the ETDRS grading system but simplified for clinical use to accommodate gradings made by clinical examination of the retina alone or when only 2-3 retinal photographs are taken (instead of the 7 fields required for the formal ETDRS grading system). In total, 35 patients (n = 26 type 2 and n = 9 type 1) with diabetes duration > 15 years, with no or only very minimal retinopathy, were studied. All patients had HbA1c measurement within 3 months of the electroretinography study. Normal Controls (n= 25) were recruited from staff or family members of patients. The absence of diabetes was confirmed by either a fasting blood glucose of < 6mmol/L or an HbA1c of < 6.0%. Although not part of the pre-planned study protocol, we also compared their RETeval-DR™ results with a group of 9 diabetic patients who also had long duration of diabetes (> 15 years) but, in contrast to the Retinopathy -ve Cohort, they were affected by

retinopathy (n = 7 moderate, n = 2 severe). This group of Retinopathy +ve Controls had the RETeval-DR™ test as part of their clinical assessment and none had laser or anti-VEGF treatment prior to the time of the test.

Results are expressed as mean+/-SD and differences between groups were tested by unpaired t test.

The study protocol was approved by the Ethics Review Committee of the Sydney Local Health Service. As the RETeval-DR™ test is not standard practice in people without diabetes, written informed consent was obtained from participants who volunteered as Normal Controls.

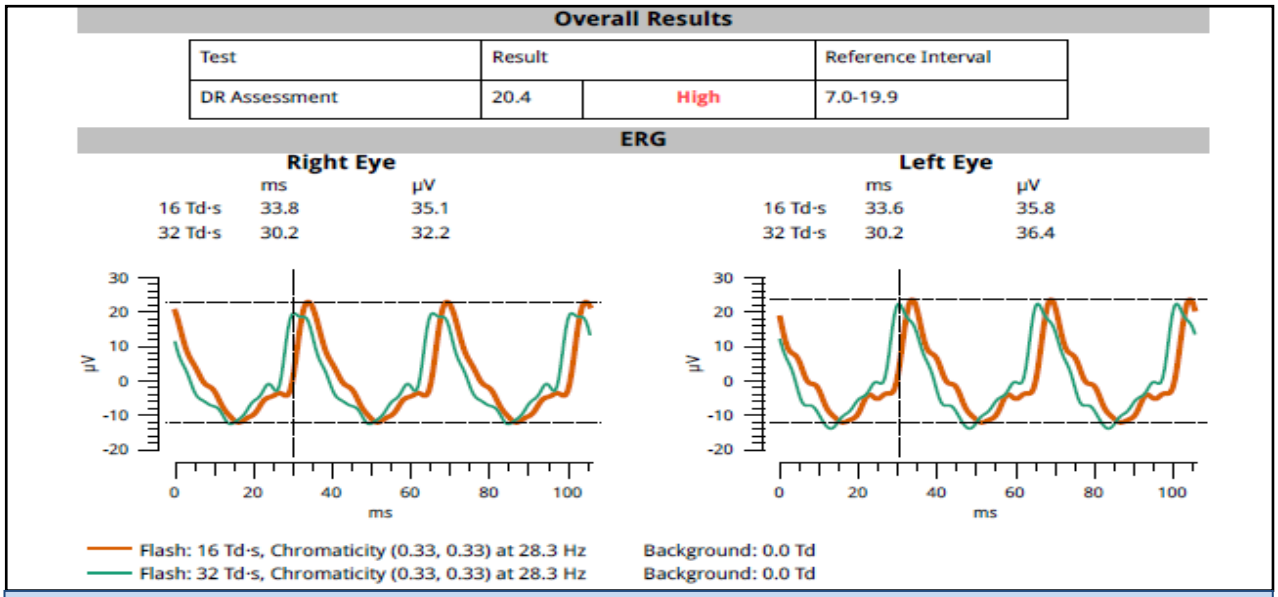

Figure 1: RETeval Device and Printout.

RESULTS

The composite score correctly identified 31/35 patients of the Retinopathy –ve Cohort as having no vision threatening retinopathy. The false positive rate of 4/35 is consistent with the specification of the manufacturer and the intention of minimizing the risk of missing significant retinopathy. Due to the design of the study, the false negative rate cannot be derived from this experimental cohort. The Implicit Time of these individuals with long duration of diabetes but no retinopathy was only minimally and not significantly longer than Normal Controls, but the Amplitude was significantly reduced by about 30%, $p < 0.01$ vs Normal Controls (Table 1).

Table 1: Electroretinographic findings of people with long duration of diabetes but no retinopathy.

	Normal Controls *n* = 25	Retinopathy -ve Cohort		
		T1D *n* = 9	T2D *n* = 26	T1D+T2D *n* = 35
Female	20/25	2/9	7/26	9/35
Age at RETeval Test (yrs)	48.9 ± 11.0	49.9 ± 10.6	67.9 ± 5.5	63.3 ± 10.6
Age of Diabetes Diagnosis (yrs)	N/A	17.1 ± 11.3	45.4 ± 6.7	38.1 ± 14.9
Duration of Diabetes (yrs)	N/A	32.8 ± 9.4	22.5 ± 4.5	25.1 ± 7.5
Composite Score	15.5 ± 2.6	17.1 ± 2.6	17.4 ± 2.5	17.3 ± 2.5
Composite Score (<20)	24/25	8/9	23/26	31/35
Implicit Time (msec)	29.4 ± 1.2	29.1 ± 1.2	30.9 ± 1.7*	30.5 ± 1.8#
Amplitude (uV)	31.8 ± 9.4	21.3 ± 6.9*	23.8 ± 4.5*	23.2 ± 5.3*
Pupil Area Ratio (mm)	2.3 ± 0.5	2.3 ± 0.6	1.9 ± 0.4	2.0 ± 0.5

Different from Normal Controls, *p<0.01, #<0.05, t-test
T1D – type 1 diabetes
T2D – type 2 diabetes

For the Retinopathy +ve Controls of nine patients with long duration of diabetes, the mean diabetes duration of 20.3 ± 4.3 years was similar to the Retinopathy –ve Cohort studied. Their mean Composite Score was 18.1±3.5 with the two individuals who had severe retinopathy correctly identified by having a Composite Score of > 20. The Implicit Time and Amplitude of the Retinopathy +ve Controls were respectively 31.5 ± 2.5 msec and 28.9 ± 7.8 uV, each in the direction of showing worse retinal function than the Normal Controls, although not statistically significant. Notably, the Amplitude of the Retinopathy +ve Controls was significantly higher (closer to normal) than the Retinopathy -ve Cohort.

DISCUSSION

Previous studies using electroretinography have shown that patients with diabetes developed demonstrable neurophysiological abnormalities of the retina after only a short duration of diabetes. Some of the studies also reported that such changes were more severe in those with retinopathy [1,2]. With the help of modern technology such as Optical Coherence Tomography, thinning of retinal nerve layers in diabetes has been demonstrated structurally and could be the basis of the functional changes. There are many possible mechanisms proposed to explain how abnormalities of retinal nerves can impact on the function of the retinal neurovascular unit, leading to microvascular changes of diabetic retinopathy [1,2]. To answer definitively the question of causality, a placebo controlled prospective study randomising some patients to receiving treatment which prevent retinal neurophysiological changes would be needed. However, this experimental design is problematic because of the dual requirements of having agent(s) with proven and appropriate retino-neuro-protective actions and a follow up period sufficiently long for retinopathy to develop. Therefore, despite the fact that the EUROCONDOR Study [2], a trial of such a prospective randomised design, showed little benefits of neuroprotection in preventing retinopathy, the relevance of neurophysiological changes in causing diabetic retinopathy is not excluded. Until definitive information is available, observational studies on diabetic patients with well-defined characteristics remain a useful source of information. This was our rationale in studying patients without retinopathy despite long standing diabetes. If neuronal changes are causally linked to retinopathy, this would be supported by finding this group of individuals to have less neurophysiological changes of the retina. To the best of our knowledge, this particular question has not been previously tested.

Our results showed these individuals with "normal" retinal microvasculature nevertheless have significantly abnormal retinal neurovascular response manifested as a 30% reduction in amplitude of electrical activity of the retinal cells. A similar loss in the composite sensory nerve action potential is a well described phenomenon of diabetic peripheral sensory neuropathy and is considered a good surrogate measure of the degree of nerve fibre loss. A similar loss of retinal nerve fibres

due to diabetes can be the basis of the lower nerve action potential we have observed, although this degree of abnormality is evidently not sufficient by itself to be associated with diabetic retinopathy. We explored the possibility that a more severe abnormality of retinal cell electrical response is required for retinopathy development. This was not substantiated by the analysis of results derived from clinical patients with longstanding diabetes who have retinopathy. In fact, their neurophysiological parameters were found unexpectedly to be more normal than individuals free of retinopathy studied by the same RETeval-DR™ technique. It is of interest that Fukuo et al., [11] had reported that the amplitude of retinal cell response can be paradoxically more normal with more severe grade of retinopathy. However, patients in our Retinopathy +ve Controls were not selected according to pre-specified criteria and the number of patients was also small because many others were excluded by prior laser or anti-VEGF treatment. Thus, the observation would need further investigation in a larger number of well-matched patients. Another possible interpretation of our results is that neurophysiological changes of the type we have observed play little role in the genesis of retinopathy. While this is possible, it is more likely, as suggested by Simo et al [2], that some pattern(s) of neurovascular interactions downstream to the development of neurophysiological changes, present in some individuals but not in others, play the pivotal role in determining the emergence of diabetic retinopathy. This is similar to the well-known observation that the same degree of peripheral sensory neuron damage will cause neuropathic pain in some but not in others, because the central transmission and filtering of abnormal nerve signals are different between individuals.

There remain considerable uncertainties about the role and the best technique for testing retinal neurophysiological changes to facilitate early detection and monitoring of diabetic retinopathy [7]. Our results showed that retinal electrophysiological changes are not direct correlates of the propensity to develop diabetic retinopathy. However, being a pilot study there are a number of limitations. Ideally, all three groups should be larger and well matched in number of participants, age and duration of diabetes. The normal range of each neurophysiological parameter should also be better defined. Clearly, more research is required. Having a more accessible and simple method of documenting retinal neurophysiology would be a significant help in this regard as clinicians/scientists in non-specialist centres can assist in collecting valuable information. Indeed this study highlights this possibility. The RETeval-DR™ is marketed as a tool for clinical screening of diabetic retinopathy with the purported advantages that the device is easy to use and provides simple numerical results which allow categorization of patients according to risk of vision threatening retinopathy. Its superiority versus the well accepted and widely available retinal photography [12] is debatable and would likely be more useful in centres with less resources and expertise in detecting and grading retinopathy. Although not a complete substitute for detailed electroretinography, the RETeval-DR™ does open the opportunity for more research on the neurophysiology of diabetic retinopathy at the bedside level. In this regard, availability of more primary data from the RETeval-DR™ for analysis would be a considerable step forward to prove the utility of this device in research, a sentiment also expressed by Fukuo et al [11].

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DATA AVAILABILITY

De-identified clinical data and results of the RETeval-DR™ printouts of the Retinopathy –ve Cohort are available from the corresponding author

CONTRIBUTION STATEMENT

BB and DKY contributed to conception and design of the study, acquisition, analysis and interpretation of data and writing of the article. YS and EL performed the RETeval-DR™ tests. All authors contribute to acquisition of data, reading and revising the manuscripts and approval of the final version for publication.

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