NEURO-MUSCULAR ELECTRICAL STUDY OF DIABETES MELLITUS

Thesis Presented To

The Faculty of Medicine, Ain Shams University

In Partial Fulfilment Of,

M.D. Neurology

By

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1968

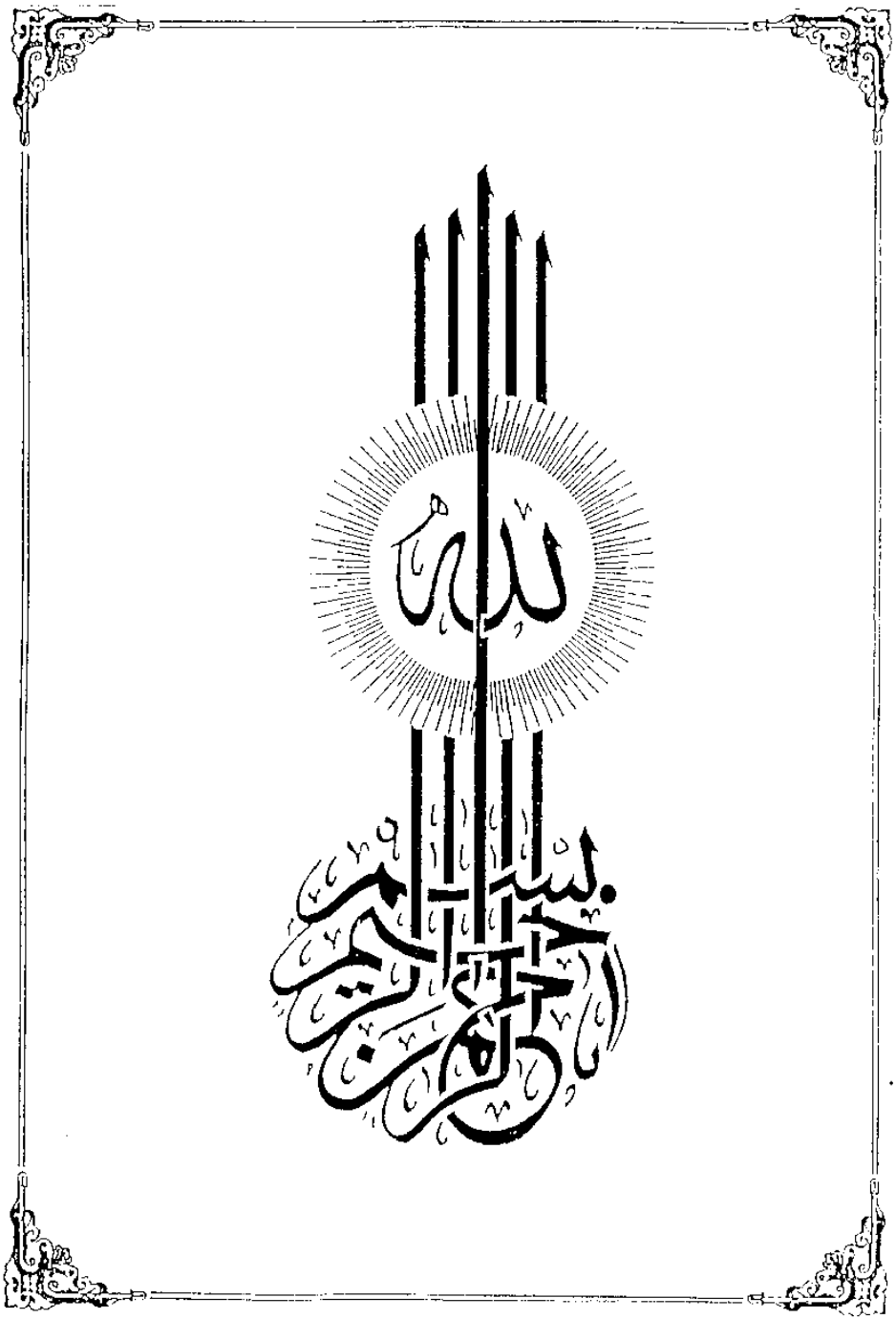
ACKNOWLEDGEMENT

I would like to express my great appreciation and gratitude to Professor Dr. Abbas H. Hassan, Professor of Neuro-psychiatry, Ain Shams University, who supervised this thesis. His invaluable advice, his supervision of the research in all its stages, his revision of all the details and discussion of all the results, have made the thesis possible.

The invaluable help and fruitful advice kindly given to me by Dr. M. Moustapha, Assistent Professor of Neuro-psychiatry, can never be estimated, and I feel greatly indebted to him.

My thanks and appreciation also go to Dr. M.E. Fadli, Lecturer of Neuropsychiatry, who offered me cordially much of his knowledge and experience, in Electromyography and nerve stimulation.

I feel indebted also to Dr. M. Alshebrawy, Head of Hygeine and Statistic Department, Mansoura, Faculty of Medicine, for his kind help and advice in the statistical part of the work.



I wish to offer my thanks also to Dr. M. Talaat Kotp, Lecturer of General Medicine, Cairo University, for his help and advice.

And last but not least I would like to express my gratitude to all members of the E.M.G. unit, Neuro-psychiatric section, Ain Shams University, and to all who contributed and helped me in this work.

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INTRODUCTION

As a disease entity diabetes mellitus has been known for thousands of years, yet its nature eludes the most intense inquiry. Indeed, it is rather surprising how very little is known about the dynamics of this most important metabolic disease.

It is quite true that much has been learned about its characteristics since man first observed ant's inordinate attraction for the urine of diabetics, and since he discovered its sweet taste. However many other problems still evade man's grasp.

Ancient Egyptians recognized diabetes mellitus since 3500 years. It was mentioned in Papyrus Ebers as abnormal increase in the volume of urine.

Aretaeus a Roman Physician (30 A.D. - 60 A.D.) was the first to introduce the name diabetes. The word means to pass through.

AVICENNA, a well known Arabian physician about 1000 A.D. gave a very complete description to the disorder including some of its complications such as diabetic gangrene, and he remarked the presence of honey like

presence in urine of diabetic patients. It is now generally accepted that diabetes is due to involvement of the nervous system.

ففى كتاب القانون لابن سينا ، ص ٩٩ فى وصفه لاعراض مرض السكـــــر ، ومضاعفاته تـــال .

"يولد فى مرضاه الطحلة (لون بين الغبرة والسواد) فتـــــــرق مراتهم ، وتحبس احشاؤهم ، وتقشف منهم الاطراف والمناكب والرقـــاب . وتغلب عليهم سهوة الاكل والعطش ، وتحبس بطونهم وتضمر ارجلهم وتضعف اكبادهم ، ويتولد فيهم الجنون ، ويعسر على نسائهم الحبل والولادة ... ويكثر للصبيان الادر وجرق السان ، ولا تبرأ قروحهم .

The genious observations of the Arabian Physician Avicenna continued to master and direct the medical science for few centuries. It is surprising that up to the 17th century, nothing was mentioned in the medical literature of Europe about the presence of sugar in urine until pancreatic origin of diabetes was described in 1889 by Hering and Minkowski.

As regards muscle and nerve investigation , it would be reasonable if more attention was paid in trying to understand the electrical events in relation to structural changes, and we feel that there must be a gradual shift, from differential emphasis on structural, or chemical events, or electrophysiological changes towards attempting at integrating all three.

As an introduction to our electrophysiological investigation, we will try to review recent trends in biochemistry, histopathology, and pathophysiology of neuromuscular system in diabetes, in order to discuss the problem of diabetic neuropathy from all its angles.

BIOCHEMICAL ASPECT:

Metabolism of diabetic muscle:

The important role of insulin on muscle metabolism is now beyond doubt. Depancreatized animals, and diabetic patients may suffer from derangement of their motor function. On the other hand muscles might continue to function apparently well, yet by more accurate recent electromyographic investigations muscular changes could be detected.

The effect of insulin on the muscle metabolism has been studied experimentally. There is marked impairment of glucose uptake in perfused diabetic muscle, (Randle 1964), (Mayer 1965). On the other hand glucose uptake in non diabetic isolated muscle is increased by increasing its concentration, (Wohltmann 1967.).

In fact the muscle membrane posseses a rather specific transport system which carries certain sugars into the cell interior, at a rate greater than could be

expected by simple diffusion. Recently this transport system has been investigated by examining the muscle membrane with electron microscopy, (Franzini 1964), (Endo 1964), (Peachy 1965). They found invaginations in the muscle membrane, and described them as transverse tubules, the lumens of which are continuous with the extracellular space. Insulin acts on this transverse tubular system, stretching the sarcolemma, and expanding pathways by which water, glucose, amino-acids enter the muscle cell.

Metabolism of nerve in diabetes:

The metabolism of nerve is greatly affected by the absence of insulin. It was found that insulin has a positive influence on O_2 consumption of peripheral nerves (Hodler 1952). At the same time insulin added in physiological amounts to normal nerves enhances glucose uptake, increases production of $C^{14}O_2$ from labelled glucose C^{14}, (Field 1966).

Diabetic nerves on the other hand appears capable of admitting normal amounts of glucose intracellularly, but there is marked limitation in conversion of glucose carbon to fatty acids which is needed for myelin construction. In addition there are accumulation of abnormal metabolic products which exerts a harmful osmotic effect,

leading to [illegible] of K^+ & Na^+ homeostatic relationship (Field 1966). This abnormal metabolism might cause structural changes, and impaired dielectrical conductivity, with functional disturbances of diabetic nerves.

CLINICAL ASPECT:

Although Aviconna about A.D. 1000 gave a sufficient description of neuromuscular disorders of diabetes, it was only on 1936, when Jordan gave a thorough account of the clinical description of these disorders.

Neurological disorders however represent an important and practical theoretical facet of diabetes mellitus. They may be the initial clinical manifestations, and may be regarded as concomitant and integral feature of diabetes, rather than a complication, (Ellenberg 1958).

Jordan 1936, separates diabetic neuropathy into "true" and "regenerative" neuritis and Sullivan 1958 into "asymmetric motor" and "Distal symmetric neuropathy", Fry 1962 into "Amyotrophy" and "Symmetrical peripheral neuropathy", Goetland 1955 and Isaac and Gilchrist 1960, considered that patients with predominantly motor involvement warranted special description. It is uncertain whether such variants represent more than one disease, as has been suggested by Sullivan 1958. However it would be

difficult clinically to satisfy fully the requirements of individual authors. Greenbaum 1964 feels that the general division of diabetic neuropathy into separate clinical syndromes, has no satisfactory basis. Patients could be described where clinical features resembled Garland's cases with motor weakness only, but in whom severe sensory loss was present. All grades of symmetry of motor weakness were seen, as well as transition from the asymmetrical to symmetrical weakness. Certain features, could not have been separated satisfactorily no matter which division was made. These included predominant localization of the neuropathy in the lower limbs, occurrence of sensory loss, tendon areflexia, and manifestation of autonomic nerve damage.

The incidence of diabetic neuropathy varies according to the criteria of its diagnosis. When the objective as well as subjective evidence of neuropathy are searched for, the incidence will be quite low. On the contrary when the symptoms alone are taken as sufficient indication of neuropathy, the frequency increases to the opposite extremes.

An initial symptom of diabetic polyneuropathy is pain. It is predominently nocturnal and disappears towards morning. Paraesthesia and hyperalgesia are also

frequent initial symptoms. Latter by ossteitis, hypo-algesia, sensory ataxia, and loss of vibration sense. The lower extremities are first affected distally (Hoffman 1964). Above the foot, polyneuropachy is ascending and progressive, (Holt 1962), the early susceptibility of the foot might be due to its distance from the heat, the length of its neurones, and insufficient collateral circulation. Impotence , and nocturnal diarrhea are widely regarded as autonomic nerve involvement in diabetes, and accordingly have been listed as neuropathic manifestations.

There is variability in the degree of muscular weakness in diabetic cases, from the slightest to a severity sufficient to prevent ordinary activities, (Greenbaum 1964). Muscular weakness is prominent among patients with untreated diabetes. Those of incipient Ketosis often complain particularly of profound weakness, and lassitude. Muscular weakness, which may progress to severe generalized paralysis, sometimes develops during recovery from diabetic coma.

Localized muscular weakness, and atrophy to a marked degree occur more frequently when one nerve is severly damaged. On the other hand primary muscular damage is rare except in areas of ischeamia due to vascular complication (Denny-Brown).

Since the description of Gerland 1953, 1955, to diabetic amyotrophy, subsequent records discussing the syndrome have appeared (Sullivan 1958), (Gerland 1960), (Isaacs 1960), (Locke and Lawrence 1963). Linden 1963 described 18 cases of diabetic amyotrophy detected in about 1800 diabetics observed for 2-5 years. Muscle biopsies were examined by some of the previous authors without any characteristic microscopic changes.

Bilateral symmetrical absence of ankle jerks are the most reliable objective criterion in the diagnosis of diabetic neuropathy, (Ellenberg 1961). The mean duration of ankle jerk in diabetic patients was found to be longer than in controls (Berdwood 1964), (Hunton 1966).

Again it would be difficult clinically to satisfy fully the requirements of individual authors, in every case of diabetic neuropathy. On the other hand patients presenting with different modes of presentation may be left at the end with similar physical signs, considering all the clinical manifestations of neuropathy to be potentially chronic in nature, (Greenbaum 1964).

PATHOGENESIS OF DIABETIC NEUROPATHY:

Attempts have been made to establish association between diabetic neuropathy, and other diabetic manifestations in order to draw a conclusion about pathogenesis.

Vascular hypothesis:

Researchs in recent years have proved that vascular changes caused by diabetes mellitus represent a specific disease which affects cheifly arterioles, capillaries, and venules. Changes of this kind have been known for some time in the vessels of the retina and kidney, as diabetic retinopathy and diabetic glomerulosclerosis respectively.

The walls of the small diabetic vessels are thickened and by electron microscopy, widening of basement membrane appears. These changes are found at the same time in the vasa nervorum, (Fagerberg 1959), (Goldenberg 1959), (Pedersen 1962), and in muscle arterioles, (Goldenberg 1959), (Aagenaese 1961), (Pedersen 1962), (Zacks 1962).

Mendlowitz 1953, Janada 1964, differentiated between 2 types of vascular changes, that called diabetic angiopathy which is a specific vascular disease,

and that arteriosclerotic process was [illegible] by diabetes.

Collyer 1961 proposed that destruction of the peripheral nerves is due to arteriosclerosis and linear calcification of the arteries in diabetes. The hypothesis of ischaemia secondary to arteriosclerosis as a cause of diabetic neuropathy has been stressed by many authors such as Needles 1943, Broch 1947, Martin 1953, Fagerberg 1956, 57, 59, 61. The ischaemic hypothesis is supported by increased incidence of neurological disability at 50 years age when arteriosclerosis also is frequent. This has been recently approved by Hedfern and Bebin 1965 who considered the vascular lesion in the nervous system of diabetics to be concomitant of arteriosclerosis and hypertension, which occur most frequent in diabetes.

In spite of this evidence much of which appearing convincing at the surface, ample research has accumulated to cast some doubt on it. Though arteriosclerotic occlusive phenomena could be observed at the vaso-nervorum, it would take a massive overwhelming affection to bring about disruption of the nerve. This however was not seen at any significant extent (Hoffman 1964). Another argument against this hypothesis is the