REVIEW IN BIOCHEMICAL & MOLECULAR CHANGES IN FRIDRICH'S ATAXIA

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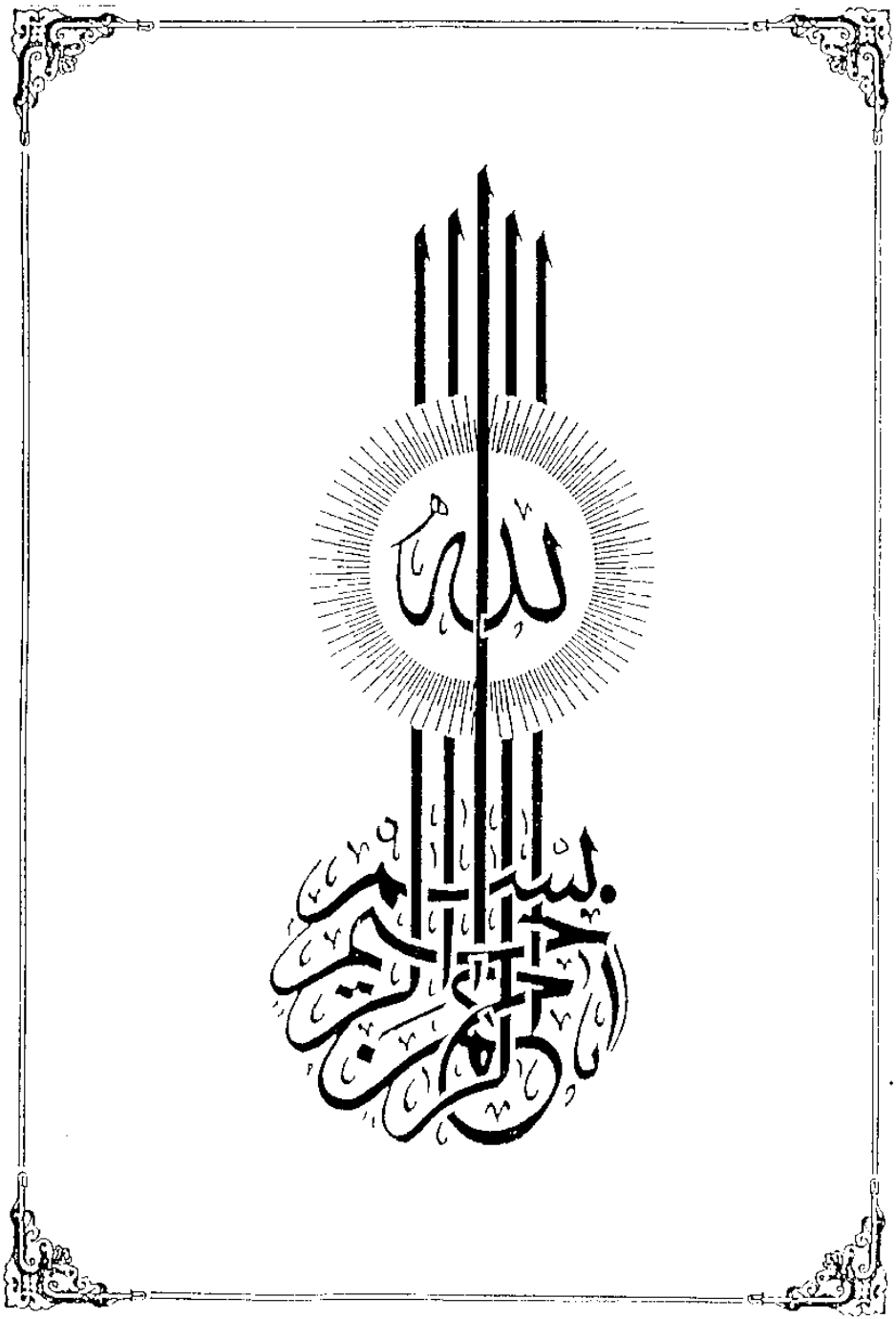

C O N T E N T S

A C K N O W L E D G E M E N T

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A B B R E V A T I O N S

BAEP : Brain stem auditory evoked potentials.

BAIB : B - amino-isobutyric acid.

CS : Cholesteryl sulfate.

ENG : Electro-nystagmo-graphy.

FAD : Flavin adenine dinucleotide.

FEP : Free erythrocyte protoporphyrin.

GDH : Glutamate dehydrogenase enzyme.

HDL : High density lipoproteins.

HGPRT : Hypoxanthine guanine phospho-ribosyl transferase.

KGDH : Ketoglutarate dehydrogenase enzyme.

Km : Kinetic motion.

LAD : Lipoamide dehydrogenase enzyme.

LDL : Low density lipoproteins.

LCAT : Lecithin cholesterol acyl transferase.

NAD : Nicotinamide adenine dinucleotide.

NADPH : Nicotinamide adenine dinucleotide phosphate.

PDH : Pyruvate dehydrogenase.

SCD : Spino cerebellar degeneration.

SEP : Sensory evoked potential.

TRH : Thyroid releasing hormone.

VDH : Valine dehydrogenase enzyme.

VEP : Visual evoked potential.

INTRODUCTION
and
AIM OF THE WORK

I N T R O D U C T I O N

Heredofamilial nervous diseases represent a challenge to neurologists. Most of these diseases are not understood regardeing their etiology and pathogenesis.

The general consensus is that they are caused by enzyme defect or and a metabolic disturbances that in the due time result in nervous manifestations.

The modern great advances in the understanding of nervous transmission parallelled with more knowledge regarding the chemical structures of the nervous system open a new era in which more understanding of these diseases will pave the way to know the pathogenesis and accordingly the managment. In this way we mention, Parkinsons disease, Refsum's disease, Macharthurs and others as a forerunners for an optimistic look in the future.

Freidreich's ataxia, with a rather well known clinical picture, among many familial cerebellar ataxias gained much interest in modern research. Authours all over the world report important findings using different approaches. The great number of research papers on this subject made it useful to review and tabulate the findings with a breif comment regarding these advances and possibly our idea about future lines in research. This is the aim of this review.

HISTORICAL PROSPECTIVES

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Aristotle first wrote of the "small brain" in the fourth century B.C.. The intricacy of its folia suggested it might have complex and important functions as the center of the mind and source of motor nerves and autonomic functions.

Galenic medicine regarded it as a source of the spinal cord and motor nerves. The vermis was considered as a value that regulated the flow of animal spirits (ventricular fluid).

Versalius provided the first modern and accurate anatomical description of the cerebellum although apparently adhering to the popular belief that it or the underlying fourth ventricle was the source of memory and intellect.

Variolio, one of the first anatomists to examine the brain after removal, first recognized the pons (pons Varolii) as a separate structure.

Willis described the three cerebellar peduncles in 1664 and Vieusseus the internal structure later in 17th centery.

Early experiments by Rolando demonestrated cerebellar control over ipsilateral motor function.

Flourens, performing more percise ablations, noted that no movements were lost with cerebellar lesions, only

ANATOMY OF THE CEREBELLUM

their coordination.

Luciana first succeded in obtaining long survival from ablative operations and developed the concept that the cerebellum acted as a single function unit. This unitarian concept persisted for about 50 years, gaining support from Sherrington who regerded it as the "head ganglion of the proprioceptive system". Andre-Thomas presented extensive studies of human cerebellar dysfunction.

Holmes raised doubt about the unitarian concept after his studies on human cerebellar lesions, and modern investigations have identified localizable function.

DEVELOPMENT OF THE CEREBELLUM: (Fig. 1).

The cerebellum first appears in the cyclo-stomes and is represented as a bridge of tissue formed by an elevation of the lateral part of the medulla oblongata, where lateral line and vestibular centeres lie.

Even in low vertebrates the cerebellum receives fibers from the medulla, tectum and spinal cord.

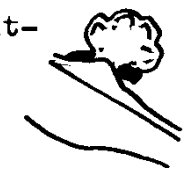
In Fishes:

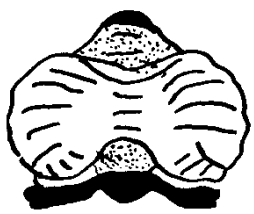
The cerebellum is differntiated into two parts, a median un paired portion anteriorly (the corpus cerebelli) and two lateral portions posteriorly (the auricles). These latter represent the vestibular part.

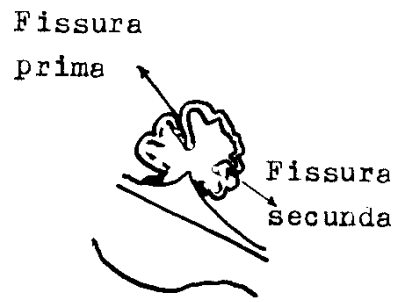
In Large Reptiles:

In which appendages are well developed, the corpus

Fig. 1.
Diagram illustrating hypothetical evolutionary stages in development of the cerebellum:
A, hypothetical primitive cerebellum;
B. reptilian cerebellum.
C. mammalian cerebellum.
The vestibular part of the cerebellum is colored black, the spinal part is stippled, and the part which develops in relation to the cerebral cortex is white. The cerebellum is represented from its dorsal aspect on the left, and in median section in the right-hand diagrams. (Courtesy of Sir W.E.L. Clark and Macmillan & Co. Ltd., London).







cerebelli is in creased in size, espicially its lateral parts, and the auricles are fused medially. It has been assumed that this early lateral enlargement in association with the development and use of appendages represents the cerebellar hemisphere in humans.

The fused auricular portions foreshedows the vestibular flocculo-nodular division of the higher cerebellums.

The corpus cerebelli with its median (vermis) and lateral parts, or (hemispheres), has gradually increased in development as the mamalian Scale is ascended, the auricular or vestibular portion is overshadowed but persists.

In Humans:

Cerebellum is formed by the proliferation of cells in the Rhombic lips of the metancephalon. They form two rounded swellings which at first project medially in the cavity of the fourth ventricle.

They are connected with the vestibular nuclei and form the most primitive cerebellum or (Archi cerebellum) It is represented in the adult cerebellum by the lingula above and the floculonodular lobe below.

The medial part of the swellings froms the future vermis while the lateral portion forms later the cerebellar hermisphers. The vermis of either side grows and fuses with that of the opposite side to form one median vermis.

In The 3rd Month:

The cerebellar hemisphere grows considerably, bulges laterally and does not project in the cavity of the fourth ventricle.

The cerebellar hemisphere is further divided by the (fissura prima) into two parts.

a) The anterior lobe in front.

b) The posterior lobe behind.

The posterior lobe is in turn occasionally divided into a middle lobe, a part that has developed in conjunction with the cerebral cortices, and a posterior division, the posterior lobe proper. This latter together with the anterior lobe composes the paleo-cerebellum.

The flocculo nodular portion is the oldest part of the cerebellum (archi cerebellum) though some of the anterior and posterior lobes should be included in this term.

Since the middle lobe develops lastly and in conjunction with the great development of the cerebral cortex, it is often called the neo cerebellum.

Larsell 1953 has des-cribed for the human cerebellum a posterior flocculonodular lobe and a corpus cerebelli, separated by the posterolateral fissure. The first to be differentiated.

Divisions of the Cerebellum:

The anterior lobe is composed of vermian divisions:

Lingula Central lobule Culmen