بسم الله الرحمن الرحيم

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بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات:
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Registry of Patients with Spinal Muscular Atrophy in a Tertiary Care Unit in Egypt

Thesis

Submitted for Partial Fulfillment of Master Degree in Neuropsychiatry Medicine

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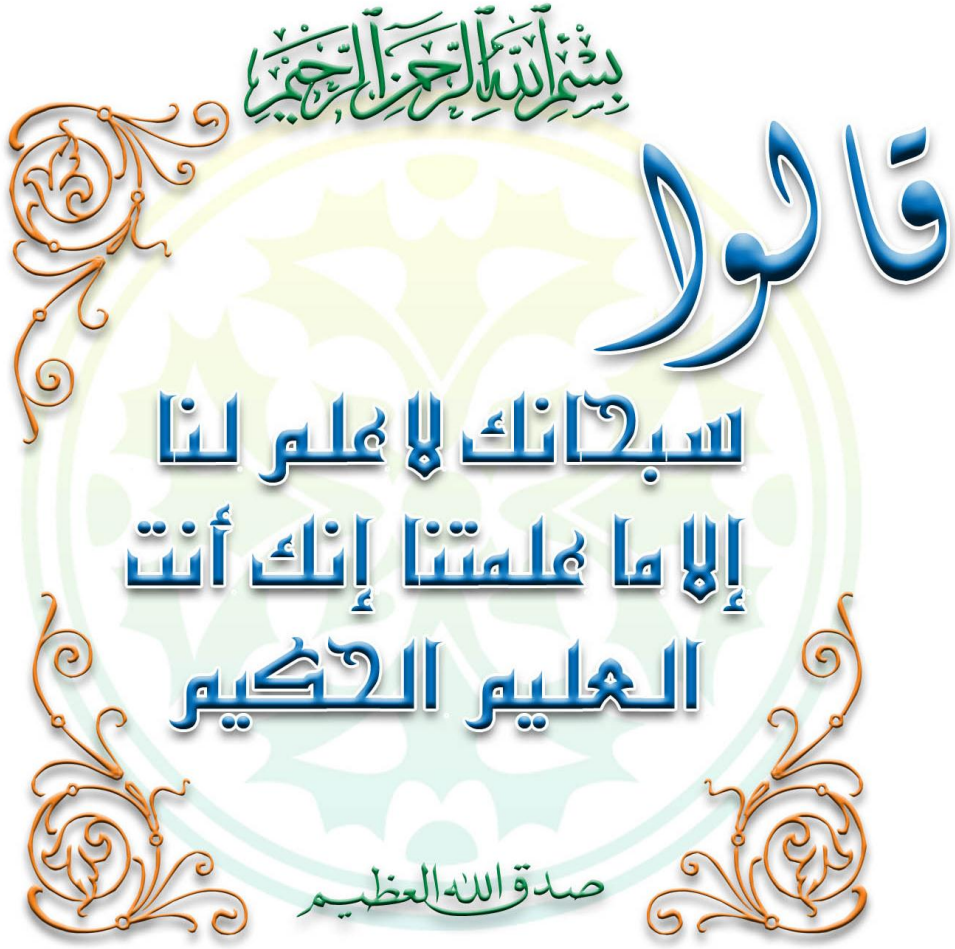

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Yosra Elsayed

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List of Abbreviations

Abb.	Full term
6-MWT	6-minute walk test
AAV	Adeno-associated viruse
BICD2	Bicaudal D cargo adaptor
CAG	Cytosine, adenine and guanine
CHOP INTEND	The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CK	Creatine kinase
DNA	Deoxyribonucleic Acid
DSMA	Distal spinal muscular atrophy
DYNC1H1	Dynein Cytoplasmic 1 Heavy Chain 1
EAPs	Expanded access programs
EMA	European Medicines Agency
EMG	Electromyography
FVC	Forced vital capacity
GMEM	Gross Motor Function Measure
HFMS	Hammersmith Functional Motor Scale
HFMSE	Hammersmith Functional Motor Scale Expanded
HINE	Hammersmith Infant Neurological Exam
HMN	Hereditary motor neuropathy
IQR	Interquartile range
MFM	Motor function meaasure
MHFMS	Modified Hammersmith Functional Motor Scale
MLPA	Multiplex ligation probe amplification
mRNA	Messenger ribonucleic acid
NCV	Nerve conduction velocity

List of Abbreviations Cont...

Abb.	Full term
NIV/IV	Non invasive ventilation/ invasive ventilation
NSAA	North Star Ambulatory Assessment
PCR	Polymerase chain reaction
PEG	Percutaneous Endoscopic Gastrostomy
PUL	Performance of upper limb
QMT	Quantitative Muscle Testing
RHS	Revised hammersmith scale
RULM	Revised upper limb module
SMA	Spinal muscular atrophy
SMA-PCH	SMA with pontocerebellar hypoplasia
SMARD	SMA with respiratory distress
SMN	Survival motor neuron
TREAT-NMD	Treat neuromuscular disease
WES	Whole exom sequencing
WGS	Whole genome sequencing
XL-SMA	X-Linked SMA

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INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease characterized by degeneration of alpha motor neurons in the spinal cord, resulting in progressive proximal muscle weakness and paralysis. The most common form of SMA (proximal form) is caused by homozygous mutations of the survival motor neuron (SMN1) gene, and the diagnostic test demonstrates in most patients the homozygous deletion of the SMN1 gene, generally showing the absence of SMN1 exon 7. This typical form is classified into four grades of severity (SMA I, SMA II, SMA III, SMA IV) based on age of onset and motor function achieved ***(Arnold et al., 2014).***

The incidence of spinal muscular atrophy is about 1 in 10,000 live births with a carrier frequency of approximately 1 in 50. Male individuals are most frequently affected, especially with the early-onset forms of spinal muscular atrophy ***(Verhaart et al., 2017).***

The clinical classification of proximal form of SMA is dependent upon age of onset and maximal level of motor function achieved. Patients with SMA type I (SMA-I) are infants diagnosed usually by 6 months of age who never achieve independent sitting. Those with SMA type II (SMA-II) present usually between six and eighteen months of age and achieve sitting but never walk independently. Those who

achieve independent ambulation have either SMA type III (SMA-III), presenting usually after eighteen months of age, or SMA type IV (SMA-IV), which presents after age 30 years ***(Montes et al., 2009).***

Other forms of spinal muscular atrophy and related motor neuron diseases, such as spinal muscular atrophy with progressive myoclonic epilepsy, spinal muscular atrophy with lower extremity predominance, X-linked infantile spinal muscular atrophy, and spinal muscular atrophy with respiratory distress type 1 are caused by mutations in other genes ***(Ikeda et al., 2017).***

Aim of the Work

Registry of patients with SMA who are diagnosed clinically and genetically (typical and atypical forms) in a tertiary care unit in Egypt.

Chapter 1

SPINAL MUSCULAR ATROPHY, AN OVERVIEW

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease characterized by degeneration of alpha motor neurons in the spinal cord, resulting in progressive proximal muscle weakness and paralysis.

It is the most common genetic cause of infant mortality, and seems to be present in practically all populations.

Spinal muscular atrophy was originally described in 2 infant brothers by Guido Werdnig in 1891 and in 7 additional cases by Johan Hoffmann from 1893 to 1900. Although the eponym Werdnig-Hoffmann disease eventually became affixed to the severe infantile form of SMA, their cases actually were of intermediate severity; the first descriptions of severe infantile SMA were made by Sylvestre in 1899 and Beevor in 1903. A milder form of SMA in which patients retained the ability to stand and walk, with prolonged survival, was not formally described until the 1950s by Wohlfart, Fez, and Eliasson and then in more detail by Kugelberg and Welander ***(Kolb et al., 2011).***

All of these descriptions recognized and emphasized the seminal pathology as anterior horn cell degeneration as well as the pertinent clinical features of symmetrical, proximal

predominant extremity weakness that also affects axial, intercostal, and bulbar musculature ***(Kolb et al., 2011).***

Epidemiology:

Most of published study results on SMA epidemiology in Europe indicate an SMA incidence of 1:8,400 births (11.9/100,000). In 2011–2015 SMA was diagnosed in 4,653 patients in Europe, with 992 cases in 2015 alone.These results are compatible with the largest study on SMA epidemiology ever initiated, which has been conducted in the USA on a multi-ethnic group of 68,478 people ***(Sugarma et al., 2012).***

This showed an SMA carrier frequency in the population of 1:54 people and an incidence of 1:11,000 births. A significant difference in carrier frequency was noted as depending on race, with the highest in Caucasians (2.02%) and the lowest in African-Americans (0.98%).

In contrast to SMA incidence, its prevalence is difficult to estimate. This is due to the various ages of onset and clinical courses of SMA which influence lifespan, additionally modified by improved standards of care, especially respiratory support.

The global register of patients (the TREAT-NMD Global SMA Patient Registry) provided data from 26 national registries, representing 29 countries and contained a total of 4,526 genetically confirmed patients. This number does not