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Role of Neuro-Sonography as Diagnostic and Differentiation Tool of Amyotrophic Lateral Sclerosis

Thesis

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Presented by

Rana Zakaria Ahmed Mohamed
Master Degree in Neurology and Psychiatry

Under Supervision of

Dr. Nagia Aly Fahmy
Professor of Neurology
Faculty of Medicine, Ain Shams University

Dr. Hytham Hamdy Salem
Associate Professor of Neurology
Faculty of Medicine, Ain Shams University

Dr. Hossam Moussa El-sayed Sakr
Professor of Radiology
Faculty of Medicine, Ain Shams University

Dr. Hossam-Eldin Mahmoud Afifi
Associate Professor of Neurology
Faculty of Medicine, Ain Shams University

Faculty of Medicine, Ain Shams University
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Rana Zakaria

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List of Abbreviations

Abb.	Full term
ALS	Amyotrophic Lateral Sclerosis
ALSFR-r	ALS functional rating scale
CK	Creatine kinase
CNS	Central Nervous System
CSA	Cross-sectional Surface Area
CSM	Cervical spondylotic Myelopathy
DM	Diabetes Mellitus
DTF	Diaphragm thickening fraction
EDx	Electrodiagnostics
EMG	Electromyography
FRS	Functional Rating Scale
HTN	Hypertension
LL	Lower Limb
LMN	Lower Motor Neuron
Lt.	Left
MMN	Multi focal Motor Neuropathy
MRC	Medical Research Council muscle scores
MRI	Magnetic resonance imaging
MUAP	Motor unit action potential
PLS	Primary Lateral Sclerosis
PN	Peripheral neuropathy
PUMN	Predominant Upper Motor Neuron
Rt.	Right
SD	Standard Deviation
UL	Upper Limb
UMN	Upper Motor Neuron
UMND	Upper Motor Neuron Disease

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INTRODUCTION

Neuro-sonography is an emerging neuro-imaging modality that allows evaluation of multiple peripheral nerves in a short time window as it often shows multifocal enlargement of nerves in demyelinating neuropathies ***(Grimm et al., 2014).*** Inflammatory demyelinating and axonal neuropathies may have distinctive sonographic patterns of nerve enlargement and appear to be influenced by treatment ***(Goedee et al., 2014).***

Ultrasonography of the peripheral nervous system is a relatively young area of interest in neurology, although it was already reported in the radiological literature in the 1980s ***(Beekman & Visser, 2004).*** It allows peripheral nerves to be visualized with excellent resolution and has proved to be reliable, effective, noninvasive and well tolerated, as many peripheral nerves run a superficial course; they are easily accessible to sonography, even very small nerves and fascicular patterns can be studied, furthermore, nerves may be examined over a long course in a few minutes (e.g. the median nerve from wrist to axilla) ***(Beekman & Visser, 2004).***

Sonography of peripheral nerves requires the use of transducers with high insonation frequencies (usually 12-15 MHz or more), normal peripheral nerves reveal a characteristic echo-texture: tubular structure with multiple hypo-echoic but discontinuous linear areas separated by hyper-echoic bands in longitudinal and multiple rounded hypo-echoic areas in a

homogeneous background in the transverse plane (fascicular or honeycomb pattern) ***(Silvestri et al., 1995).*** Nerve sonography can demonstrate five main pathological changes:

(i) Nerve enlargement,

(ii) Increased hypo-echogenicity or hyperechogenicity,

(iii) Enlarged fascicles,

(iv) Increased thickness of the epineurium and

(v) Increased endoneural/perineural blood flow ***(Boom & Visser, 2012).***

The cross-sectional area (CSA) of nerves should be measured within the hyper-echogenic rim at multiple sites and in order to demonstrate nerve enlargement, measurements should be performed and compared with a set of reference values ***(Cartwright et al., 2008).*** Multiple studies have demonstrated nerve enlargement in both mononeuropathies and polyneuropathies ***(Beekman et al., 2011).***

Polyneuropathies could be either inflammatory or degenerative; Inflammatory polyneuropathy include diseases like the Multifocal Motor Neuropathy (MMN) ***(Meuth & Kleinschnitz, 2010),*** and Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) ***(Simmons et al., 1993),*** while the degenerative polyneuropathy include diseases like Motor

Neuron Disease (MND) ***(Loewenbrück et al., 2016)*** and Charcot-Marie Tooth Disease (CMT) ***(Yiu et al., 2015).***

Neuromuscular ultrasound (US) is a noninvasive, painless, and radiation-free complementary imaging technique for the diagnostic work-up of PN ***(Gallardo et al., 2015).***

Early studies in Amyotrophic Lateral Sclerosis (ALS) showed marked abnormalities with ultrasound, including reduced muscle thickness, increased muscle echo intensity, and fasciculations ***(Arts et al., 2008).*** Ultrasound also shows promise `as a biomarker of disease progression ***(Lee et al., 2010).***

Amyotrophic lateral sclerosis (ALS) is defined by progressive weakness that results from neurodegeneration of upper (UMN) and lower motor neurons (LMN); the variable mix of UMN and LMN signs produces major phenotypic heterogeneity in ALS patients ***(Ravits & La Spada, 2009).*** Thus, clinical manifestations of ALS exist on a continuum, ranging from apparently pure LMN dysfunction to severe pyramidal impairment with minor LMN signs ***(Sabatelli et al., 2013).***

Recently, there has been increasing acceptance of those distinct groups with upper versus lower motor neuron predominant pathology persisting through the course of the disease ***(Soraru et al., 2010).***

Briefly, classic ALS is characterized by the combination of LMN and pyramidal signs, upper motor neuron dominant (UMND) ALS by pyramidal signs (spinobulbar spasticity) associated with slight LMN dysfunction ***(Gordon et al., 2008),*** lower motor neuron disease or syndrome (LMND) by absence of UMN signs, and progressive bulbar palsy (PBP) by dysarthria and dysphagia ***(Karam et al., 2010).***

Exclusive UMN involvement with predominant spinobulbar spasticity is the hallmark of primary lateral sclerosis (PLS) ***(Tartaglia et al., 2007).*** Recognition of these variants can be relevant to counseling on prognosis, drug therapy, and tailoring care to the needs of the individual ***(Pupillo et al., 2014).***

Neuromuscular ultrasound abnormalities may aid in the diagnosis of ALS ***(Natalia et al., 2019),*** and also in distinguishing between ALS phenotypes (e.g., UMND vs. PLS patients), which has major prognostic implications ***(Soraru et al., 2010).***

Recently, nerve sonography has been applied to amyotrophic lateral sclerosis (ALS) demonstrating evidence of both nerve root and distal peripheral nerve atrophy ***(Schreiber et al., 2016);*** this offers potential for ultrasound-based differentiation of ALS and ALS-mimicking disorders characterized by enlarged nerves ***(Loewenbruck et al., 2016).***

In ALS, nerve enlargement has, however, never been detected and the authors describe a normal or even reduced cross-sectional area (CSA) of upper extremity nerves and a reduced diameter of the cervical nerve roots ***(Nodera et al., 2014).***

Recent study investigated whether peripheral nerve sonography could be used as a biomarker to monitor disease progression in amyotrophic lateral sclerosis (ALS), in this study High-resolution sonography appears to be a valid tool demonstrate ongoing ulnar nerve atrophy in ALS ***(Schreiber et al., 2016).***

Muscle ultrasound can facilitate and accelerate diagnosis of ALS by increasing the field of view for detecting fasciculations at a higher sensitivity in bulbar muscles, e.g. the tongue and thoracic muscles ***(Grimm et al., 2014).*** However, in some instances, differentiation from other disorders may be difficult, in particular multifocal motor neuropathy (MMN). Although MMN is rare, differentiation from ALS is essential with regard to treatment and prognosis as MMN is a treatable polyneuropathy affecting peripheral motor nerves, often following the distribution of individual nerves without involvement of sensory nerve fibers ***(Nobile-Orazio, 2001).*** MMN diagnosis is based on high titres of anti-ganglioside(G)M1-immunoglobulin M antibodies and finding of (multifocal) conduction blocks outside of common nerve entrapment sites ***(Nobile-Orazio et al., 2013)*** without signs of

UMN involvement so it's diagnosis can be difficult in early stages with absence of conduction block.

Ultrasound of the peripheral nervous system proves to be a useful additional diagnostic tool for diagnosis of hereditary neuropathies ***(Zaidman et al., 2013),*** and acquired immune-mediated acute and chronic neuropathies ***(Grimm et al., 2014).*** In MMN, focal nerve enlargement has already been previously described in ultrasound and magnetic resonance imaging studies ***(Kerasnoudis et al., 2014).*** In contrast, pronounced generalized or multifocal nerve enlargement has not been described in ALS to date, actually several authors have even described a reduction of nerve CSA or nerve root diameter as a sign of atrophic nerves ***(Nodera et al., 2014).***

The pathophysiology of nerve enlargement in MMN is not yet clear while in chronic demyelinating neuropathies, re and demyelination (onion bulbs) may play a role, while in acute and sub-acute neuropathies, focal edema and inflammation seem to cause nerve enlargement ***(Grimm et al., 2014).*** In addition, the time course of nerve enlargement and nerve atrophy in both diseases remains quite unclear so far. In CIDP, several changes of nerve CSA, echogenicity and cervical nerve root diameter depending on disease duration have been described so sonography can be used as differentiating tool between CIDP & MMN with comparing the focal enlargement of CIDP versus the focal enlargement in MMN ***(Padua et al., 2014).***