Recent advances in the critical care management of ischemic stroke, role of recombinant tissue plasmiogen activator when to use and when not to use

Essay

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By

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بسم الله الرحمن الرحيم
قالوا
سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم
صدق الله العظيم
سورة البقرة الآية: ٣٢

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Ibrahim Abd Allah El-Sayed Atiya

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List of Abbreviations

Abbr.	Full-term
ACA	: Anterior cerebral artery
ADC	: Apparent diffusion coefficient
AHA	: American Heart Association
AIS	: Acute Ischemic Stroke
AMI	: Acute Myocardial Infarction
APSAC	: Anisoylated purified streptokinase activator complex
aPTT	: Activated partial Thromboplastin time
ATP	: Adenosine triphosphate
CT	: Computed tomography
DVT	: Deep Vein Thrombosis
DWI	: Diffusion-weighted imaging
ECASS	: European Cooperative Acute Stroke Study
ECT	: Ecarin clotting time
ED	: Emergency department
EIC	: Early ischemic changes
FDA	: Food and Drug Administration
FLAIR	: Fluid-attenuated inversion recovery
GdnBzoNph	: Guanidino benzoate
GISSI	: Gruppo Italiano per la Sperimentazione della Streptochinasi nell'Infarto Miocardico
GP	: Glycoprotein
ICA	: Internal carotid artery
INR	: International neutralization ratio
IV	: Intravenous
M5	: Mutant of prourokinase

MCA : Middle cerebral artery
MI : Myocardial infarction
MRI : Magnetic resonance imaging
NCCT : Non contrast CT
NIHSS : National Institutes of Health Stroke Scale
NINDS : Neurologic Disorders and Stroke
NMDA : *N*-methyl-D-aspartate
OACs : Oral anticoagulants
PCA : Posterior cerebral artery
PE : Pulmonary embolism
PI : Prescribing information
r-PA : Recombinant plasminogen activator
rpro-UK : Recombinant pro-urokinase
SAH : Subarachnoid hemorrhage
SCD : Sickle cell disease
sICH : Symptomatic intra-cerebral hemorrhage
STEMI : ST myocardial infarction
TIA : Transient ischemic attack
TNK : Tenecteplase
tPA : Tissue plasminogen activator
TT : Thrombin time
WHO : World Health Organization

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Introduction

According to the World Health Organization (WHO), 15 million people suffer stroke worldwide each year. Of these, 5 million die, and another 5 million are left permanently disabled ***(Mackay and Mensah, 1995)***.

Between 2012 and 2030, total direct medical stroke-related costs are projected to increase to 184.1 billion **$**, with the majority of the projected increase in costs arising from those 65 to 79 years of age ***(Ovbiagele et al., 2013).***

Fibrinolytics (ie, rt-PA) restore cerebral blood flow in some patients with acute ischemic stroke and may lead to improvement or resolution of neurologic deficits. Unfortunately, fibrinolytics may also cause symptomatic intracranial hemorrhage. Other complications include potentially hemodynamically significant hemorrhage and angioedema or allergic reactions. Therefore, if the patient is a candidate for fibrinolytic therapy, a thorough review of the inclusion and exclusion criteria must be performed. The exclusion criteria largely focus on identifying risk of hemorrhagic complications associated with fibrinolytic use ***(Adams et al., 2007).***

An rt-PA stroke study group from the National Institute of Neurologic Disorders and Stroke (NINDS) first reported that the early administration of rt-PA benefited carefully selected patients with acute ischemic stroke. The FDA subsequently approved the use of rt-PA in patients who

met NINDS criteria. In particular, rt-PA had to be given within 3 hours of stroke onset and only after CT scanning had ruled out hemorrhagic stroke ***(National Institute of Neurological Disorders and Stroke, 1995).***

Subsequently, fibrinolytic therapy administered 3-4.5 hours after symptom onset was found to improve neurologic outcomes in the European Cooperative Acute Stroke Study III (ECASS III), suggesting a wider time window for fibrinolysis ***(Hacke et al., 2008).***

On the basis of these and other data, in May 2009 the AHA/ASA revised the guidelines for the administration of rt-PA after acute stroke, expanding the window of treatment from 3 hours to 4.5 hours to provide more patients with an opportunity to benefit from this therapy ***(Wahlgren et al., 2008), (Jauch et al., 2013).***

Researchers found that administration of alteplase within 4.5 hours of stroke onset significantly improved outcomes, irrespective of age or stroke severity, with earlier treatment providing the greatest benefit. The odds of a good stroke outcome were 75% higher for patients who received alteplase within 3 hours of symptom onset compared with those who did not. Patients given alteplase 3 to 4.5 hours after symptom onset had a 26% increased chance of a good outcome, and patients with a delay of more than 4.5 hours in receiving alteplase treatment had a nonsignificant 15% increase in the chance of a good recovery ***(Brooks, 2014).***

Aim of the Work

- Is to highlight the role of RTPA in the management of acute ischaemic stroke and decreasing it‘s complications.
- Provide evidence based practice guidelines for stroke care.
- Support early intervention in stroke management and develop a consistent approach to stroke care.

Points of discussions:

- Pathophysiology of acute stroke.
- Use of thrombolytic therapy in acute stroke.
- Guidelines for use of recombinant tissue plasminogen activator.

Chapter 1:
Pathophysiology of ischaemic Stroke

Epidemiology

Stroke is the leading cause of disability and the fourth leading cause of death in the United States ***(Towfighi and Saver, 2011).***

Epidemiologic studies indicate that 82-92% of strokes are ischemic. According to the World Health Organization (WHO), 15 million people suffer stroke worldwide each year. Of these, *5 million die, and another 5 million are left permanently disabled* ***(MacKay and Mensah, 2012).***

Race-, sex-, and age-related demographics

Black races have an age-adjusted risk of death from stroke that is 1.49 times that of white races. Hispanic races have a lower overall incidence of stroke than white and black races but more frequent lacunar strokes and stroke at an earlier age.Men are at higher risk for stroke than women; white men have a stroke incidence of 62.8 per 100, 000, with death being the final outcome in 26.3% of cases, while women have a stroke incidence of 59 per 100, 000 and a death rate of 39.2% ***(Schneider et al., 2004).***

Although stroke often is considered a disease of elderly persons, one third of strokes occur in persons younger than 65 years. Risk of stroke increases with age, especially in patients older than 64 years, in whom 75% of all strokes occur ***(Towfighi and Saver, 2011).***

Brain Anatomy

The brain is composed of 3 main structural divisions: the cerebrum**,** the brainstem**,** and the cerebellum (see the images below). At the base of the brain is the brainstem**,** which extends from the upper cervical spinal cord to the diencephalon of the cerebrum. The brainstem is divided into the medulla**,** pons**,** and midbrain. Posterior to the brainstem lies the cerebellum ***(Rughani et al., 2015).***

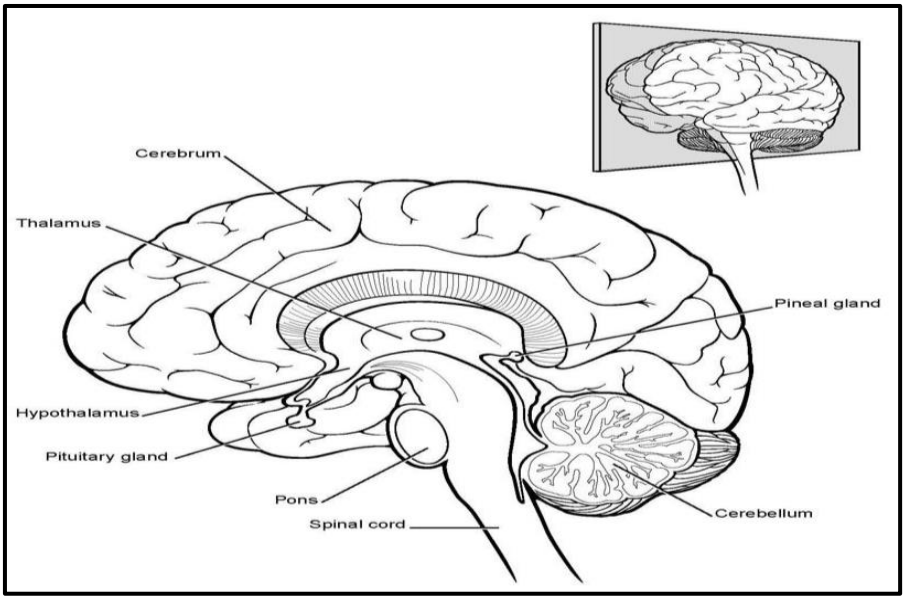

Figure (1): Brain – Midsagittal view ***(Rughani et al., 2015)***

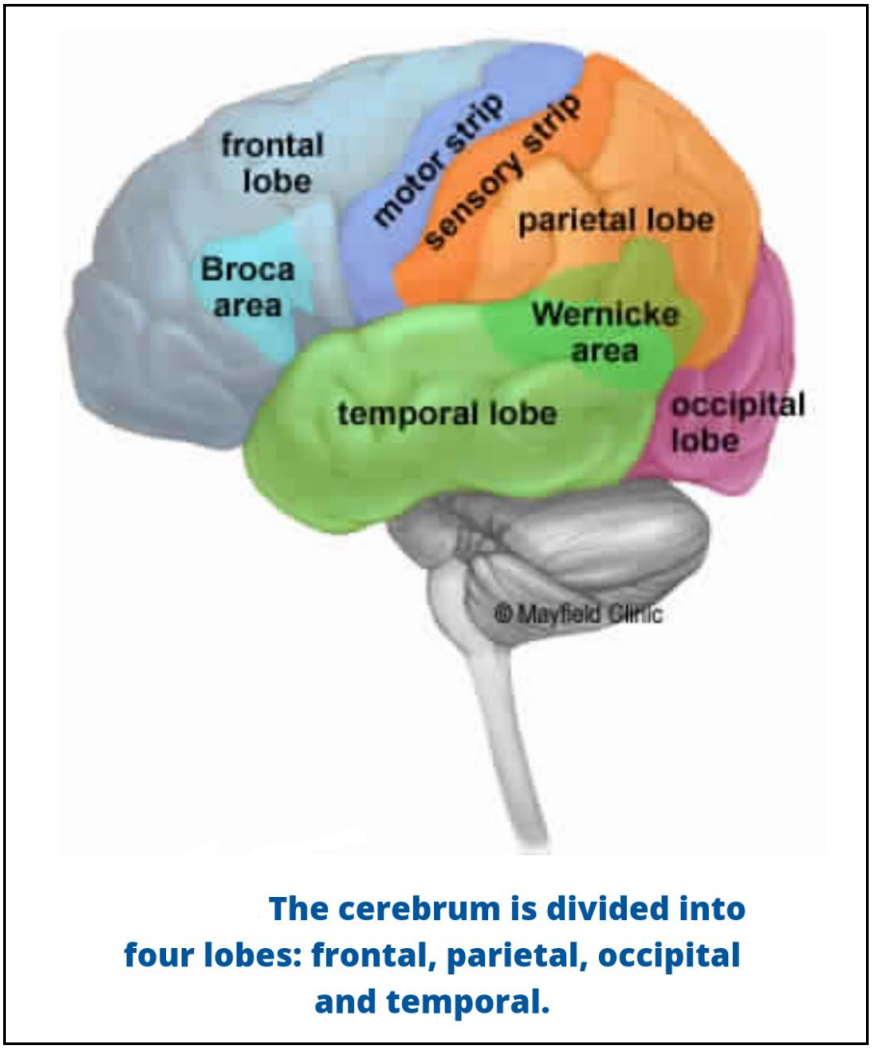

Figure (2): The four lobes of cerebrum ***(Rughani et al., 2015).***

Brain Arterial distributions

Table (1): Vascular Supply to the Brain **(Sadatomo et al. 2015)**

VASCULAR TERRITORY	Structures Supplied
Anterior Circulation (Carotid)	
Anterior Cerebral Artery	**Cortical branches:** medial frontal and parietal lobe **Medial lenticulostriate branches:** caudate head, globus pallidus, anterior limb of internal capsule
Middle Cerebral Artery	**Cortical branches:** lateral frontal and parietal lobes lateral and anterior temporal lobe **Lateral lenticulostriate branches:** globus pallidus and putamen, internal capsule
Anterior Choroidal Artery	Optic tracts, medial temporal lobe, ventrolateral thalamus, corona radiata, posterior limb of the internal capsule
Posterior Circulation (Vertebrobasilar)	
Posterior Cerebral Artery	**Cortical branches:** occipital lobes, medial and posterior temporal and parietal lobes **Perforating branches:** brainstem, posterior thalamus and midbrain
Posterior Inferior Cerebellar Artery	Inferior vermis; posterior and inferior cerebellar hemispheres
Anterior Inferior Cerebellar Artery	Anterolateral cerebellum
Superior Cerebellar Artery	Superior vermis; superior cerebellum