Lecture Four

Multiple Sclerosis

{ ومن لم يذق مرّ التعلُّمِ ساعةً.. تجرع ذلَّ الجهل طوال حياتهِ }

Revised by

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Red: Important. Grey: Extra Notes Doctors Notes will be in text boxes

Objectives:

The student should:

- Appreciate the critical role of myelin in maintaining the integrity of the CNS system.
- Understand the pathogenesis and the clinic-pathological features of multiple sclerosis as the classical and the commonest example of CNS demyelinating diseases.

Key principles to be discussed:

- Myelin function
- The differences between CNS and PNS Myelin
- Primary Demyelinating disease classification
- Multiple sclerosis: definition, epidemiology, pathogenesis and clinicopathological features; with special emphasis on CSF analysis findings, morphology and distribution of MS plaques.

Take home messages:

- In view of the critical role of myelin in nerve conduction; diseases of myelin can lead to widespread and severe neurologic deficits.
- Diseases of myelin can be grouped into demyelinating diseases (in which normal myelin is broken down for inappropriate reasons-often by inflammatory processes), and dysmyelinating diseases (which are metabolic disorders that include the leukodystrophies in which the underlying structure of the myelin is abnormal or its turnover is abnormal).
- Multiple sclerosis, an autoimmune demyelinating disease, is the most common disorder of myelin, affecting young adults often with a relapsing-remitting course and eventual progressive accumulation of neurologic deficits.
- Other less common forms of immune-mediated demyelination often follow infections and are more acute illnesses.

References:

Lecture, Robbins, First aid Step 1

MULTIPLE SCLEROSIS

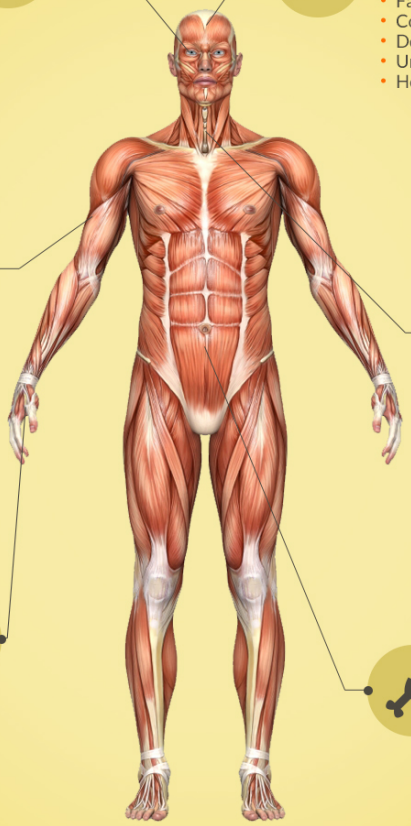
PORTRAIT OF A PATIENT

VISION

- Involuntary Eye Movement
- Vision Loss
- Abnormal Eye Alignment
- Double Vision

CENTRAL NERVOUS SYSTEM

- Fatigue
- Cognitive Impairment
- Depression
- Unstable Mood
- Hearing Loss



MUSCULAR SYSTEM

- Muscle Atrophy
- Muscle Spasms
- Lack of Muscle Coordination

THROAT AND SPEECH

- Slurring
- Stuttering
- Difficulty Swallowing

SENSORY SYSTEM

- Heightened Pain
- Reduced Sense of Touch
- Constant Sense of Tingling and Burning

DIGESTION

- Incontinence
- Diarrhea

POSSIBLE CAUSES OF MS

IMMUNOLOGIC

MS causes damage to the protective fatty coating that surrounds nerve cells (Myelin), causing signals from the cells to slow down or stop all together.

ENVIRONMENTAL

Being exposed to greater amounts of sunlight year-round and higher levels vitamin D help protect against autoimmune diseases like MS.

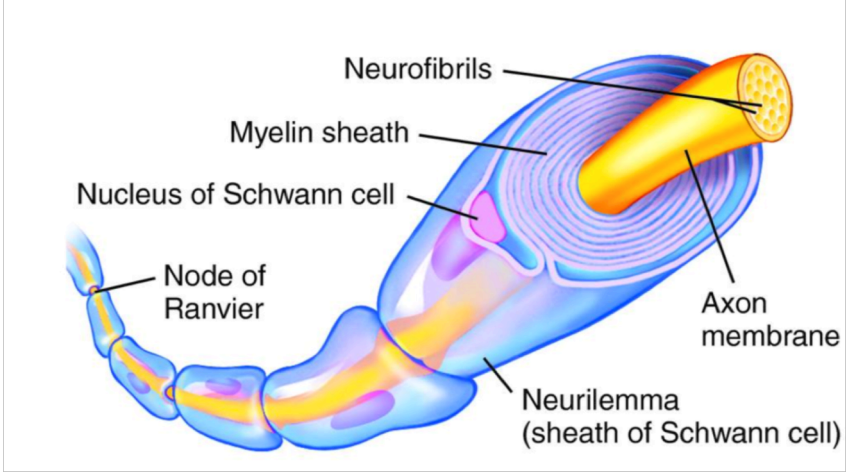
INFECTIOUS

Exposure to measles, canine distemper, epstein-barr, and pneumonia during childhood are a common triggers for later development of MS.

GENETIC

MS is not hereditary in a traditional sense, however having a relative with MS increases the risk of developing the disease significantly.

Key Principle: Myelin Function:



- Myelin consists of multiple layers of the specialized plasma membrane of oligodendrocytes (in the CNS), with most of the cytoplasm excluded.
- Myelinated axons are present in all areas of the brain, they are the dominant component in the white matter; therefore, most diseases of myelin are primarily white matter disorders.
- An oligodendrocyte extends processes toward many different axons and wraps a segment of roughly a few hundred microns of axon.
- Each of these segments is called an *internode*, and the gaps between internodes are known as *nodes of Ranvier.*

Doctor's Question: What is the function of myelin?

The main purpose of a myelin layer (or sheath) is to increase the speed at which impulses propagate along the myelinated fiber. Along unmyelinated fibers, impulses move continuously as waves, but, in myelinated fibers, they "hop" or propagate by saltatory (jumping) conduction.

Key Principle: The differences between CNS and PNS Myelin:

CNS	PNS
Myelinated by oligodendrocytes	**Myelinated by Schwann cells**
Each cell myelinates many axons and forms many internodes	**Each cell myelinates only one axon and forms only one internode**
Do not form neurilemma	**Forms neurilemma**

Neurilemma is the cytoplasm and nuclei of the Schwann cells which lie outside the myelin sheath. They are important in nerve regeneration, which is why CNS axons have limited regeneration.

The myelin in peripheral nerves is similar to the myelin in the CNS but:

- The specialized proteins and lipids are also different.
- Most diseases of CNS myelin do not significantly involve the peripheral nerves, and vice versa.

Doctor's Question: What is "The natural history of a disease?"

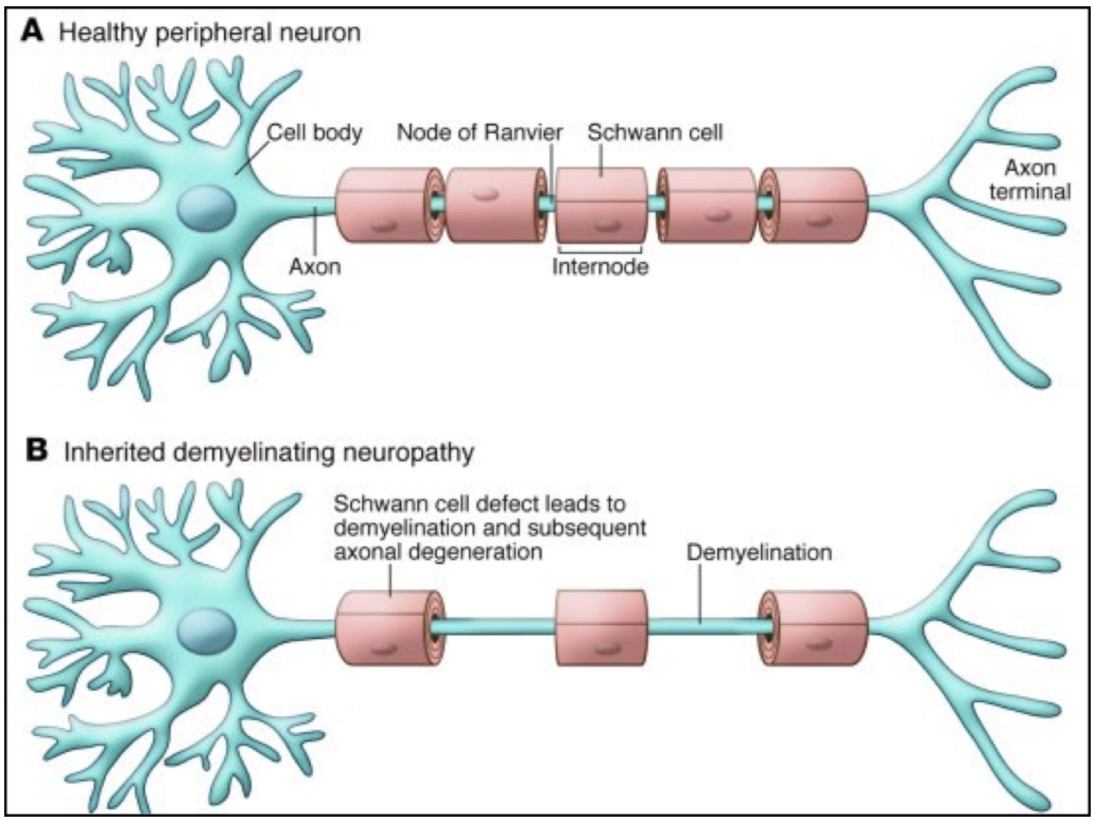
The natural history of **disease** is **the course** a **disease** takes in individual people from its pathological onset (inception) until its eventual resolution through complete recovery or death.

التاريخ الطبيعي للمرض هو المسار الذي يسلكه المرض في الأفراد من البداية المرضية حتى زوال المرض سواء كان الزوال بالتعافي الكامل او الموت

The natural history of demyelinating diseases is determined, in part, by the limited capacity of the CNS to regenerate normal myelin and by the degree of secondary damage to axons that occurs as the disease runs its course.

تاريخ المرض يتحدد جزئياً بقدرة الجهاز العصبي المركزي المحدودة على إعادة تكوين خلايا مايلين طبيعية وعلى درجة الأضرار الثانوية للأكسون التي تحدث أثناء مهاجمة خلايا الدم البيضاء لطبقة المايلين.

Key Principle: Primary demyelinating disease general classification:



Two broad groups:

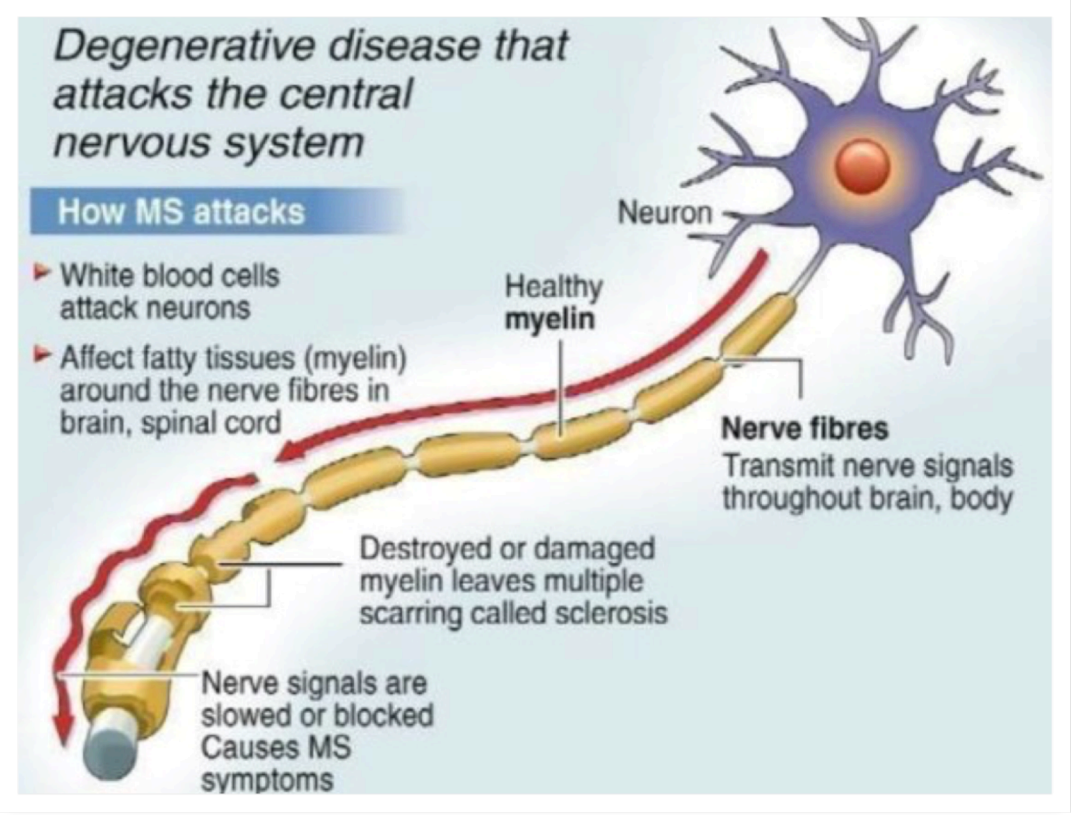
A. *Demyelinating diseases* of the CNS:

- Acquired conditions characterized by preferential damage to previously normal myelin
- Commonly result from immune-mediated injury
- Also viral infection of oligodendrocytes as in progressive multifocal leukoencephalopathy.
- Drugs and other toxic agents.

B. *Dysmyelinating diseases* of the CNS:

- Myelin is not formed properly or has abnormal turnover kinetics[1]
- Associated with mutations affecting the proteins required for formation of normal myelin or in mutations that affect the synthesis or degradation of myelin lipids.
- The other general term for these diseases is *leukodystrophy.*

Key Principle: Multiple sclerosis:



[1] Formation and absorption.

Definition:

MS is an autoimmune demyelinating disorder characterized by *distinct episodes of neurologic deficits, separated in time* **(نوبات عصبية مفصولة بالزمن)** *attributable to white matter lesions that are separated in space* **(مفصولة بالمكان، تحدث في أماكن مختلفة)**

Epidemiology:

- The most common demyelinating disorders (prevalence of 1 per 1000 persons in most of the United States and Europe)
- The disease becomes clinically apparent at any age, although onset in childhood or after age 50 years is relatively rare
- Women are affected twice as often as men

But in women the prognosis is better than men

- In most individuals with MS the illness shows **relapsing (عودة المرض) and remitting (فترة المعافاة)** episodes of neurologic deficits. The frequency of relapses tends to decrease during the course of the illness, but there is a steady neurologic deterioration[2] in a subset of patients.

Risk Factors:

- The risk of developing MS is 15-fold higher when the disease is present in a first-degree relative
- The concordance rate for monozygotic twins is approximately 25%, with a much lower rate for dizygotic twins
- A significant fraction of the genetic risk for MS is attributable to HLA-DR variants, the DR2 allele being the one that most significantly increases the risk for developing MS

[2] The process of becoming progressively worse.

Pathogenesis:

Like other autoimmune diseases, MS is believed to be caused by a combination of environmental and genetic factors that result in a loss of tolerance to self-proteins → **Antigen presenting cell comes and activates T-helper (CD4)** → secret cytokines IL2 and IL7 → T cell cross BBB → **Type IV hypersensitivity** → infiltrate of lymphocytes, macrophages, B Cells and plasma cells produce antibody → **demyelination**, **axonal loss** and sometimes even leading to neuronal death.

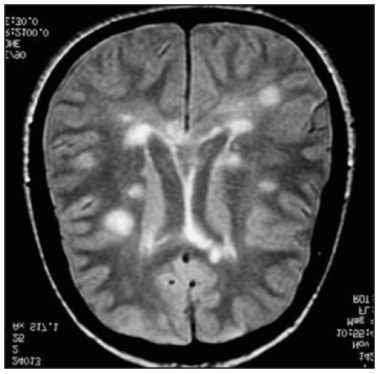
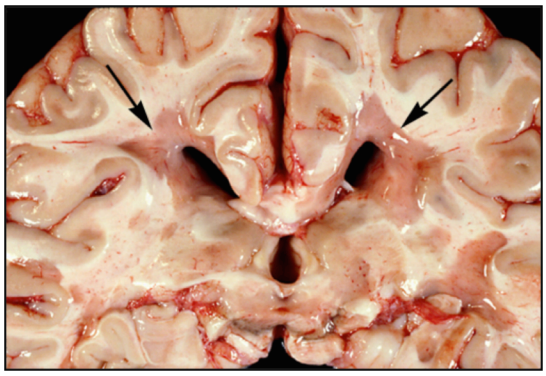
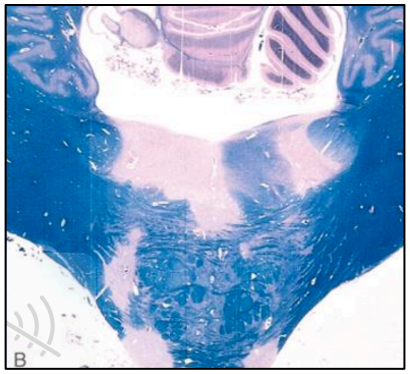
Experimental allergic encephalomyelitis:

It's an animal model of MS in which demyelination and inflammation occur after immunization with myelin, myelin proteins, or certain peptides from myelin proteins.

In this model, the lesions are caused by a T cell-mediated delayed type hypersensitivity reaction to myelin proteins, and the same immune mechanism is thought to be central to the pathogenesis of MS.

يعني اللي يسوونه هو انهم يجيبون فار ويحقنونه بمايلين او بروتينات في تركيب المايلين، جسم الفار وان كان يحتوي على مايلين بشكل طبيعي راح يعامل المايلين اللي تم حقنه به كـ Antigen وهنا راح يبدأ الجهاز المناعي حقه يهاجم المايلين المحقون ويلخبط بينه وبين المايلين المتواجد بشكل طبيعي في جسمه، فيدمر الاثنين ويصير عنده MS

Morphology:

- MS is a white matter disease.
- Affected areas show multiple, well circumscribed, slightly depressed, glassy, gray-tan, irregularly shaped lesions, termed **plaques**.
- They occur beside ventricles and they are frequent in the optic nerves and chiasm, brain stem, ascending and descending fiber tracts, cerebellum and spinal cord.
- The lesions have sharply defined borders at the microscopic level. (We use Luxol Fast Blue Stain to detect MS).

Active plaques (During the episode)	Inactive plaques
• There is evidence of ongoing myelin breakdown with abundant macrophages containing myelin debris • Lymphocytes and monocytes are present, mostly as perivascular cuffs. تجمع الخلايا حول الأوعية الدموية • Axons are relatively preserved, although they may be reduced in number.	• When plaques become quiescent[3], the inflammation mostly disappears, leaving behind a little to no myelin. • Instead, astrocytic proliferation and gliosis are prominent

[3] In a state or period of inactivity or dormancy.

Clinical features:

- The course of MS is variable. MS lesions can occur anywhere in the CNS → may induce a wide range of clinical manifestations.
- Commonly there are multiple episodes of new symptoms (*relapses*) followed by episodes of recovery (*remissions*); typically, the recovery is not complete.
- The consequence of this pattern of relapsing-remitting disease is the gradual, often stepwise, accumulation of increasing neurologic deficits. The patient dies from pneumonia

Certain **patterns** of neurologic symptoms and signs are commonly observed:

- Unilateral visual impairment occurring over the course of a few days is a frequent initial manifestation of MS (due to involvement of the optic nerve *"optic neuritis"*)
- When this occurs as the first event, only a minority (10% to 50%) go on to develop full-blown MS
- Involvement of the brain stem produces cranial nerve signs and ataxia, and can disrupt conjugate eye movements
- Spinal cord lesions give rise to motor and sensory impairment of trunk and limbs, spasticity, and difficulties with the voluntary control of bladder function.
- Changes in cognitive[4] function can be present, but are often much milder than the other findings.
- In any individual patient it is hard to predict when the next relapse will occur; most current treatments aim at decreasing the rate and severity of relapses rather than recovering lost function.

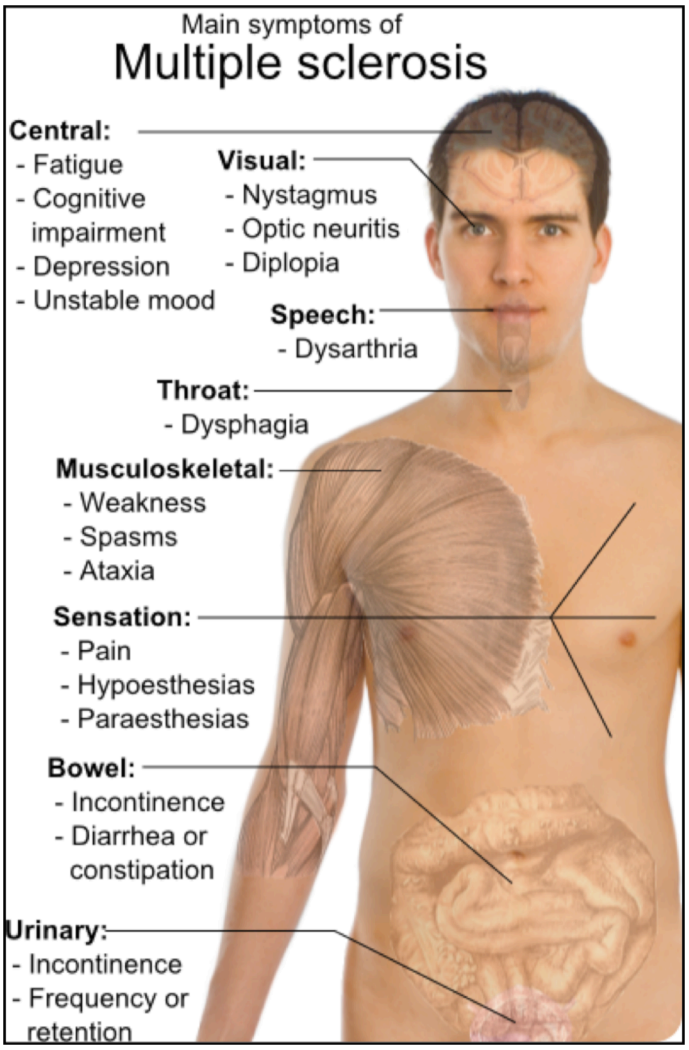
Charcot classic triad of MS is a **SIN**:

Scanning speech

Intention tremor

Nystagmus

4 ادراك



CSF findings:

- It shows mildly elevated protein level with an increased proportion of γ-globulin
- In one-third of cases there is moderate pleocytosis. (Increased WBC count in CSF, in the blood it's called Leukocytosis)
- When the immunoglobulin is examined further, most MS patients show *oligoclonal bands*, representing antibodies directed against a variety of antigenic targets. (Oligoclonal bands are proteins called immunoglobulins. Their presence indicates inflammation of the CNS. They may be a sign of MS)
- These antibodies constitute a marker for disease activity.

Radiological findings:

1- Corpus callosum will be thinner
2- Periventricular calcification

Treatment: (Extra)

Slow progression with disease-modifying therapies (e.g., β-interferon, natalizumab). Treat acute ares with IV steroids. Symptomatic treatment for neurogenic bladder (catheterization, muscarinic antagonists), spasticity (baclofen, $GABA_B$ receptor agonists), pain (opioids).

Check Your Understanding

T or F:

1- Most diseases of CNS myelin do not significantly involve the peripheral nerves.
2- In people who have a *Dysmyelinating disease,* there was a time when they had normal Myelin.
3- Under the microscope we use special stain for MS: Luxol fast blue (LFB).
4- CSF findings will show mildly elevated protein level and decreased proportion of γ-globulin.
5- MS is strongly associated with HLA-DR2.
6- In inactive plaques there is Astrocytic proliferation with inflammation.

1-T 2-F 3-T 4-F 5-T 6-F

MCQs:

1- Dysmyelinating Characterized by preferential damage to _____ myelin:

A- Not properly formed
B- Previously normal
C- Abnormal turnover kinetics
D- A & C

2- CSF findings in MS:

A- moderate pleocytosis
B- oligoclonal bands
C- elevated protein level
D- All of them

3- There is ongoing myelin breakdown in?

A- Active plaque
B- Inactive plaque
C- Both

4- MS symptoms may be caused by:

A- Damage to myelin (the sheath covering the nerve fibers)
B- Damage to axons (the nerve fibers themselves)
C- Both A & B

1. D 2. D 3. A 4. C

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	نورة الخراز
	هديل الغرير

قال صلى الله عليه وسلم: {من سلك طريقًا يلتمس فيه علمًا سهَّل الله له بهِ طريقًا إلى الجنة}

دعواتنا لكم بالتوفيق