para proteinemic neuropathies

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- **Monoclonal gammopathies are common in general population**
- Occur in 10% of patients with peripheral neuropathy
- Must able **to determine** whether association exists between the **Para protein** and **neuropathy**
- **Clinical phenotype** of **neuropathy** and **type** of **paraprotein** provides clues for diagnosis

- ***Optimal management of paraproteinemic neuropathy*** *require evaluation of monoclonal protein for underlying hematologic disorder*

Monoclonal Gammopathies

- **Monoclonal gammopathies** (M-protein):are produced by B-lymphocytes or plasma cells
- They comprise :1-(heavy chains: IgG-IgA-IgM)
- 2-light chain (kappa-lambda)
- **Monoclonal proteins are common** (3% individual older 50 years and 5% over 70 years)
- **The most common monoclonal gammopathies *IgG***

TABLE 8-2 Overrepresentation of Immunoglobulin M Paraprotein in Patients With Neuropathy[a,b,c]

Paraprotein	Frequency of Heavy Chains in Patients With Monoclonal Gammopathy of Undetermined Significance	Frequency of Heavy Chains in Patients With Monoclonal Gammopathy of Undetermined Significance and Peripheral Neuropathy
Immunoglobulin M	15%	48%
Immunoglobulin G	73%	37%
Immunoglobulin A	12%	15%

[a] Reprinted with permission from Ramchandren S, Lewis RA, Curr Neurol Neurosci Rep.[6] © 2011, Springer Science and Business Media, LLC. *link.springer.com/article/10.1007/s11910-011-0237-4.*

[b] Data from Gosselin S, et al, Ann Neurol.[10]

[c] Data from all patients with monoclonal gammopathy of undetermined significance evaluated at Mayo Clinic Rochester from 1961 to 1988.

Evaluation for monoclonal protein peripheral neuropathy

- ***Monoclonal protein commonly co-occur in peripheral neuropathy***
- ***Presence of MCP doesn't imply causatily of neuropathy***
- **Neuropathies associated with paraproteinemias include:**

➢ ***1-distal acquired demyelinating symmetric neuropathy*** *with* ***M-protein(DADS-M)***

➢ ***2-waldenstrom macroglobulinemia***

- 3-**M.M(multipel myeloma)**
- *4-**POEMS**:polyneuropathy –organomegaly-endocrinopathy-monclonal plasma cell disorder – skin changes*
- ***5-primary systemic amyloidosis***

- ***The history and electro diagnostic testing are helpful***
- ***Accompanying systemic symptoms raise concern for primary systemic amyloidosis or POEMS***
- ***Autonomic symptoms*** *are common in primary systemic* ***amyloidosis***
- ***Sensory predominant neuropathy*** with ***ataxia and IgM*** protein usually indicate **DADS-M**

ELECTRODIAGNOSTIC FEATURES

- 1- ***demyelination*** are common seen of DADS-M and POEMS
- 2- ***axonal*** :primary systemic amyloidosis-M.M-waldenstrom

- ***Monoclonal protein type** can be a clue diagnosis*

- **M.M**-is **IgG** more IgA
- ***Monoclonal gammopathy** of Undetermined significance(**MGUS**)and **waldenstrom** :are **IgM kappa***
- ***Immunoglobulin light chain** **AL amyeloidosis** :is **lambda***
- ***POEMS** **syndrome** :almost **lambda***

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TABLE 8-1 **Hematologic Disorders Associated With Paraproteins**

Hematologic Disorder	Most Common Monoclonal Protein Type	Peripheral Neuropathy Phenotype	Electrodiagnostic Phenotype
Immunoglobulin M–monoclonal gammopathy of undetermined significance (IgM-MGUS)	IgM kappa	Distal large fiber sensory predominant neuropathy with sensory ataxia	Demyelinating with prolonged distal latencies
Waldenström macroglobulinemia	IgM kappa	Distal large fiber sensory predominant neuropathy with sensory ataxia	Axonal greater than demyelinating (with prolonged distal latencies)
Multiple myeloma	IgG more often than IgA	Length-dependent sensory, sensorimotor, or motor neuropathy	Axonal
Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome	IgG or IgA, lambda	Sensorimotor polyradiculoneuropathy (chronic inflammatory demyelinating polyradiculoneuropathy [CIDP]-like)	Demyelinating
Immunoglobulin light chain (AL) amyloidosis	Lambda	Sensorimotor peripheral neuropathy with prominent autonomic involvement	Axonal

Laboratory evaluation for a monoclonal gammopathy

The evaluation for monoclonal protein in patients with peripheral neuropathy should include :

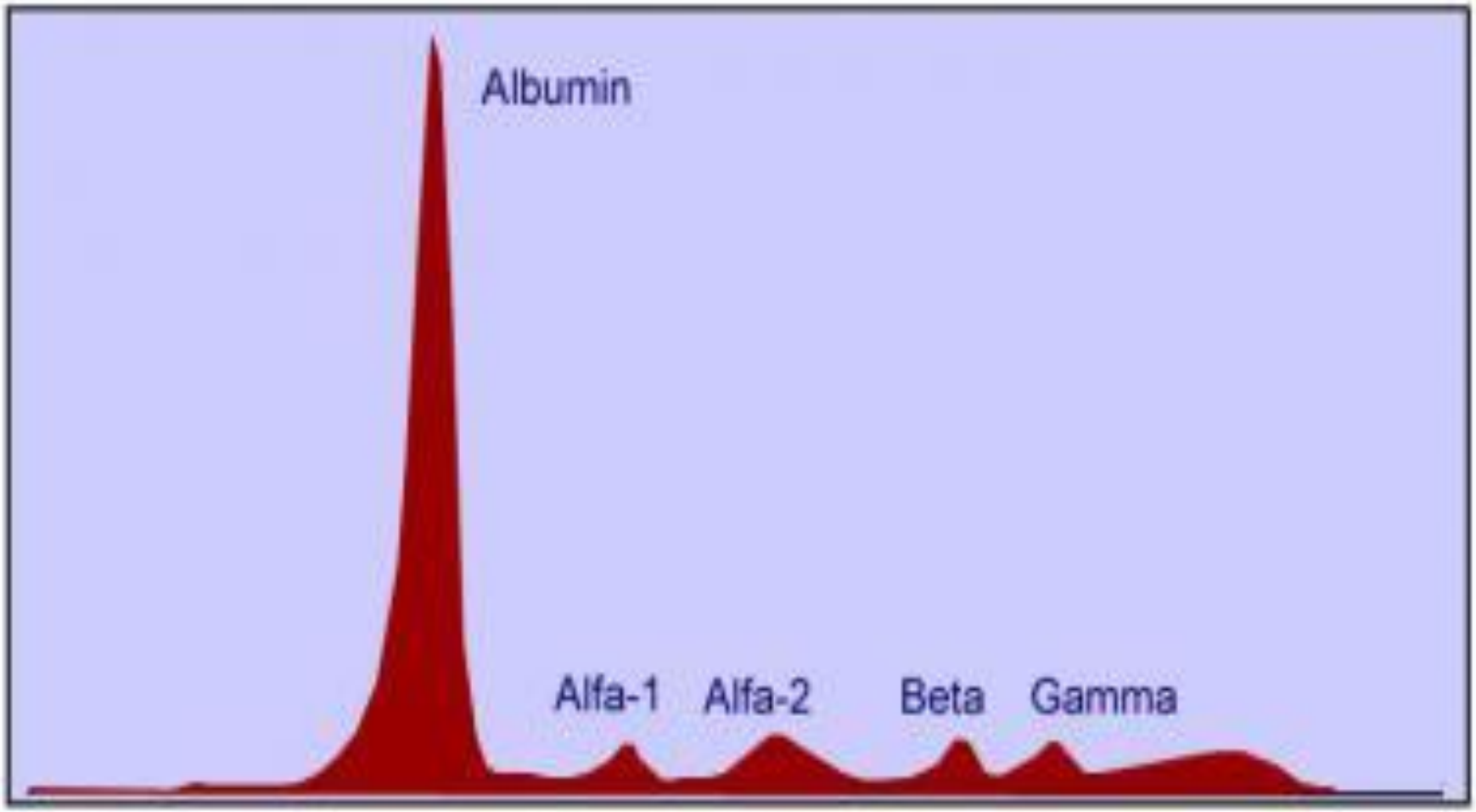
1-serum protein electrophoresis

2-serum immunofixation electrophoresis

3- *M-protein should be quantified in serum-(urine)24 hours*

4-blood cell count

5-serum calcium-creatinine levels



Normal serum protein electrophoresis diagram with legend of different zones

Monoclonal gammopathy of undetermined significance(MGUS)

- ***MGUS:****is a condition in which abnormal protein known as monoclonal protein or M-protein in blood (produced in plasma cell in bone marrow)*
- ***High risk factors*** :
- 1-***M-protein*** of 15g/L or greater
- 2-***elevated kappa/lambda(light chains)***
- ***3-non -IgG*** PROTEIN

MGUS- NEUROPATHY

- ***Up to one-third** of patients with MGUS have* *peripheral neuropathy*
- ***IgM is** the monoclonal gammopathy most*

often associated with neuropathy

Specific neuropathy phenotype of IgM is DADS-M

IgM ***typically kappa light chain***

- ***Typically affects men in 6-9 decat***
- ***Involves large sensory nerve fibers* leading to *assonsory ataxia* –mild distal *weakness***
- ***50% of patients have anti body to MAG(myelin associated glycoprotein)***

Investigation for MGUS neuropathy

***Electrophysiological feature of DADS are demyelination*:**

- ***Prolonged distal latencies***
- ***Motor conduction velocities are slowed***
- ***Sensory potentials are reduced or absent***

Electrophysiological hall mark of IgM neuropathy is prolonged distal latencies(*implying terminal nerve involvement)*

Management of MGUS neuropathy

Patients with CIDP and coexisting (IgA-IgG)

MGUS response to therapies for CIDP

In contrast :cases associated with IgM*(have less motor weakness-sensory involvement – sensory ataxia)****are less responsive to therapy than typical CIDP***

- ***In IgM associated neuropathy (DADS-M)****: no evidence to use of immunotherapy*
- ***However :in some cases used*** **(IVIG –plasma exchange-cytotoxic agent)*-response in individual patients***
- ***Ritoximab:has been considered*** (*anti CD20 activity*)

Adverse effects of Ritoximab

- ***1-fatal infusion reaction***
- ***2-mucocutaneous reaction***
- ***3-progressive muti focal leuko encephalopathy***
- ***4-re activation of hepatitis B***

PMLE:***more common in who received anther treatment***

The risk is reduced *when anti body to* ***JC*** *virus absent*

- ***All patients should screened for hepatitis B***
- ***Treatment of IgM –related neuropathy (DADS):***
- **Should be reserved for**:
- *1-younger patients*
- *2- older patients with sever weakness or gait dysfunction*

Monitoring of MGUS

- *1% of MGUS patients annually transform to M.M or serious B cell disorder*
- *Patients should be monitored with serum free light chains ratio at 6 months*
- *Urine protein electrophoresis should be assessed if an M spike was found*

Waldenstrom macroglobulinemia

- ***Waldenstrom macroglobulinemia*** :is an ***IgM associated lympho palsmacytic lymphoma***
- **Present in seventh decat**
- **Men >women (2/1)**
- **Annual incidence** *:4 per million* /per year
- **Survival is greater than 5 years**

- ***Clinical manifestation**: **hepatomegaly** **splenomegaly-lymphadenopathy-hyperviscosity***
- ***The most common symptoms :fatigue related to anemia***
- **Poor prognosis:1- *age > 65 years* – 2-anemia— 3-*thrombcytopenia* –4-elevated IgM level-5-elevated B2 microglobalin**

- **Neuropathy in waldenstrom *is clinically in distinguish able from(IgM- MGUS*)**
- ***Most common symptoms*** *:numbness of feet and gait ataxia followed tremor*
- ***Electro physiologic findings for waldenstrom neuropathy are more axonal than demyelinating***
- ***Only 27% demyelinating versus 62%in IgM MGUS***

Laboratory findings in waldenstrom

- **IgM levels** (median 3100 mg /dl)
- In **IgM-MGUS** (median 650 mg/dl
- ***Much greater presence of anemia (clues diagnosis***
- ***Patients with IgM lev*els** > *4000mg/dl :risk for hyper viscosity syndrome*
- **Bone marrow biopsy :lympho plasmacytic infiltration**
- **CT**:organomegaly-lymphadenopathy

Treatment of waldenstrom

- **Is** ***directed at patients with advanced symptoms(cytopenia - hyper viscosity)***
- ***Treatment:*** *alkylating agents –possibly in combination with rituximab*
- ***Patients with early disease***(*anemia-thrombocytopenia-hemolytic anemia-glomerulonephritis –peripheral neuropathy –my be offered ritoximab*

Multiple myeloma

***MM:** is plasma cell neoplasm of bone marrow that secretes a monoclonal protein*

Average onset is 66 years

Annual incidence :3-4 per 100.000

Cardinal features :

1-Hypercalcemia-2-reanal insufficiency-3-anemia

Most common features: fatigue –bone pain-recurrent infection

Survival is more than 8 years with current treatment

Neuropathy in MM

is common in patients with MM

it occur due to

- ***1- disease it self***
- ***2-from treatment of MM***

MM-associated perineuropathy

- ***Clinicaly**:Can be found in 5-20%of patients with untreated MM*
- ***NCS**:may increasing the incidence to up 39% with untreated MM*
- **Peripheral neuropathy :sensory-motor- sensorimotor**
- ***Most cases**: gradually progressive-length – dependent sensorimotor -neuropathy*

- ***All sensory modalities are involvement***
- ***Ankle reflex reduced or absent***
- **Neither –pain-autonomic involvement is prominent**
- ***NCS:****mild slowing of motor conduction* velocities and low to absent CMP
- ***Sensory action potential –****low to absent*

Treatment-emergent peripheral neuropathy

- ***It is the most common complication with MM***
- ***Affect up 65% of patients receiving chemotherapy***
- ***The type of neuropathy and reversibility depend on the agent used***
- ***The most common medication***
- ***1-brotezomib***
- ***2-thalidomide***

Thalidomide induced neuropathy

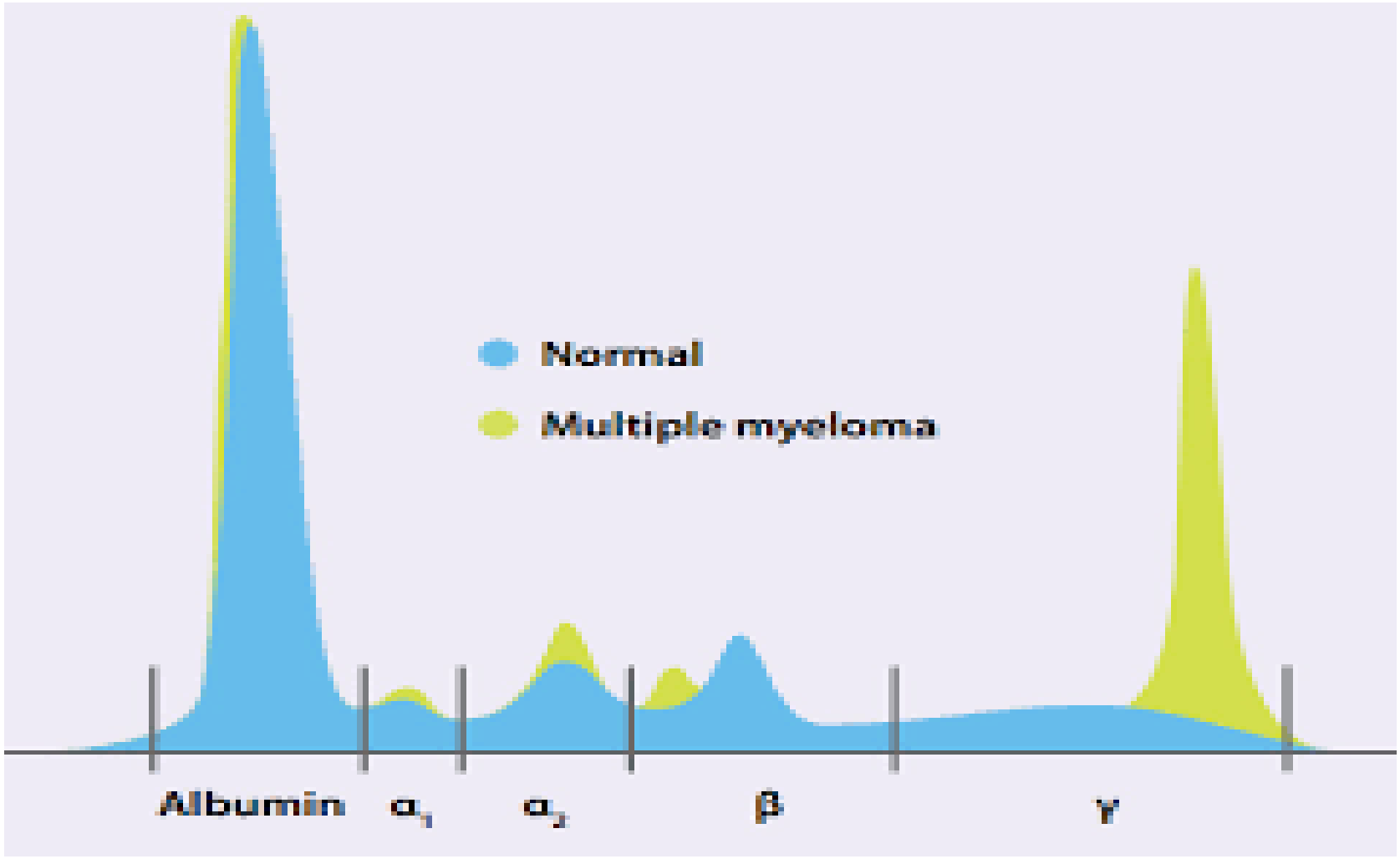
- **May occur in 58-81%of patients with MM** *and depend on the dose and treatment duration*
- ***The neuropathy is usually sensory predominant***
- ***Symptoms include*** *:painful paresthesia -numbness*
- ***Symptoms can present*** *after treatment has stopped*
- **May progress for months after stopped thalidomide**

- ***NCS:*** ***reduced sensory nerve action potential amplitude***
- ***The severity and reversibility*** ***of neuropathy depends on the length of treatment and cumulative dose***

investigation

Diagnosis of MM requires

- ***10% or more plasma cell on bone marrow examination***
- ***Or biopsy proven plasmacytoma***
- ***M protein in serum or urine***
- ***Evidence of end organ damage(hyper calcemia-renal insufficiency –anemia)***


Normal
Multiple myeloma
Albumin
α1
α2
β
γ

management

- *1- in the case of MM associated peripheral neuropathy : the treatment is to treat the plasma cell disorder*
  - *Current treatment* :
  - *1-autologous stem cell transplantation*
  - *2-chemotherapy*
- *In case treatment –emergent peripheral neuropathy*
  - *- dose reduction or removal agents when possible*