HELSE BERGEN
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UNIVERSITETET I BERGEN
Mitochondrial Medicine & Neurogenetics (MMN) group

POLG disease through all the ages

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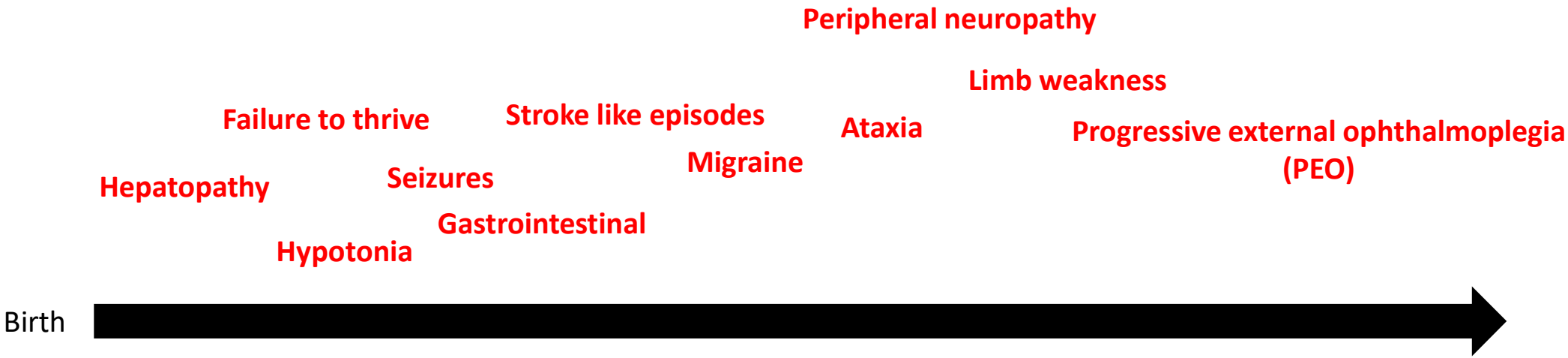
- Mutations in *POLG* are the most common single gene cause of inherited mitochondrial disease
- Clinically associated with a wide spectrum of clinical manifestations ranging from devastating fatal and neonatal disease to mild late onset disease with myopathy and progressive external ophthalmoplegia
- Diagnosis is challenging owing to clinical heterogeneity and overlap between syndromes

Mitochondrial polymerase gamma

- *POLG* is a nuclear gene, encoding the catalytic subunit of mitochondrial DNA-polymerase gamma (polγ)
- polγ is the only DNA polymerase within the mitochondrion of the animal cells that replicates and repairs the mitochondrial genome
- Mutations in *POLG* cause secondary mtDNA damage in the form of quantitative depletion, multiple deletions and increased load of point mutations. This results in respiratory chain dysfunction and impaired ATP production

POLG disease

A spectrum of overlapping phenotypes



Overlapping phenotypes with wide variation in the age of disease onset
Almost all organ systems can be affected

Saneto & Naviaux Dev Disabil Res Rev 2010
Hikmat et al JIMD 2020

Systems often involved

Central nervous system

Psychosis
Depression
Hallucination (visual)

Seizures / status epilepticus
Ataxia
Hypotonia
Stroke-like episodes
Migraine-like headache
Encephalopathy
Cortical blindness

Musculoskeletal system

Ptosis
PEO
Myopathy
exercise intolerance

Liver

Liver dysfunction/failure

The eye

Cataract
Retinopathy

Gastro-intestinal system

Faltering growth
Gastro-intestinal dysfunction

Peripheral neuropathy

Axonal sensory neuropathy

Saneto & Naviaux Dev Disabil Res Rev 2010
Hikmat et al JIMD 2020

The major clinical features according to different age categories

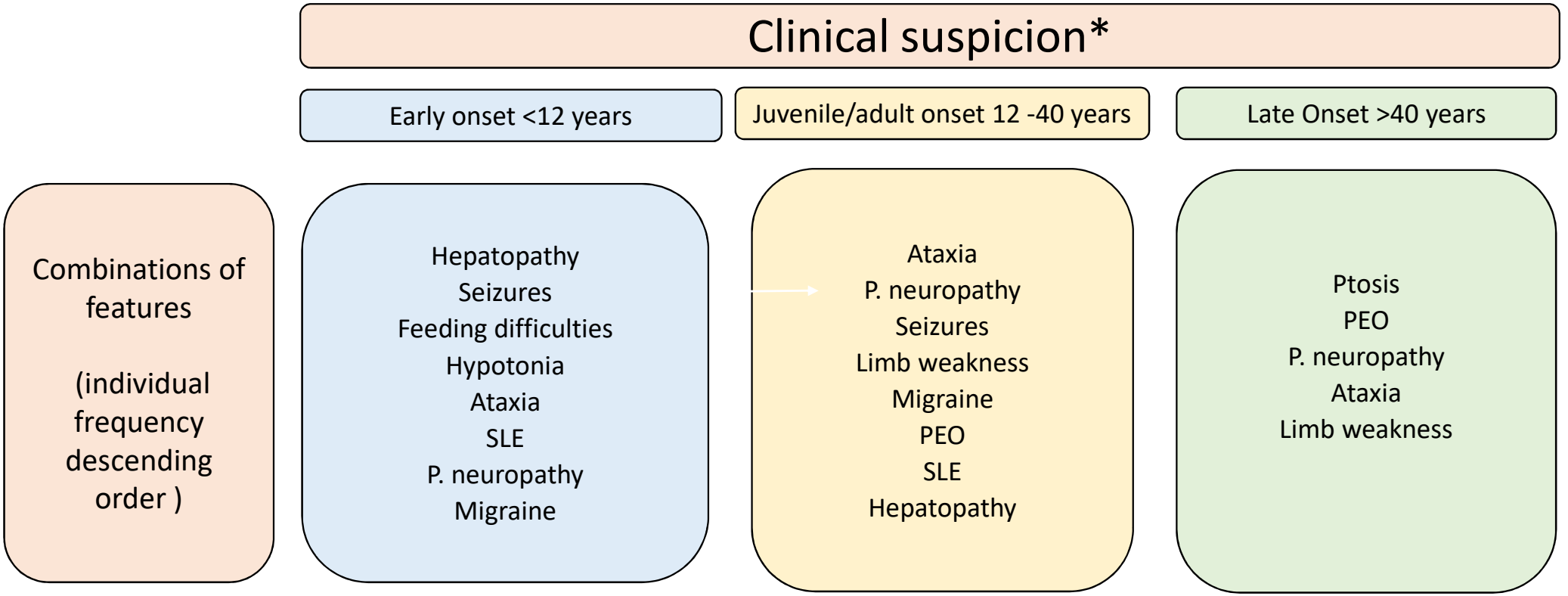
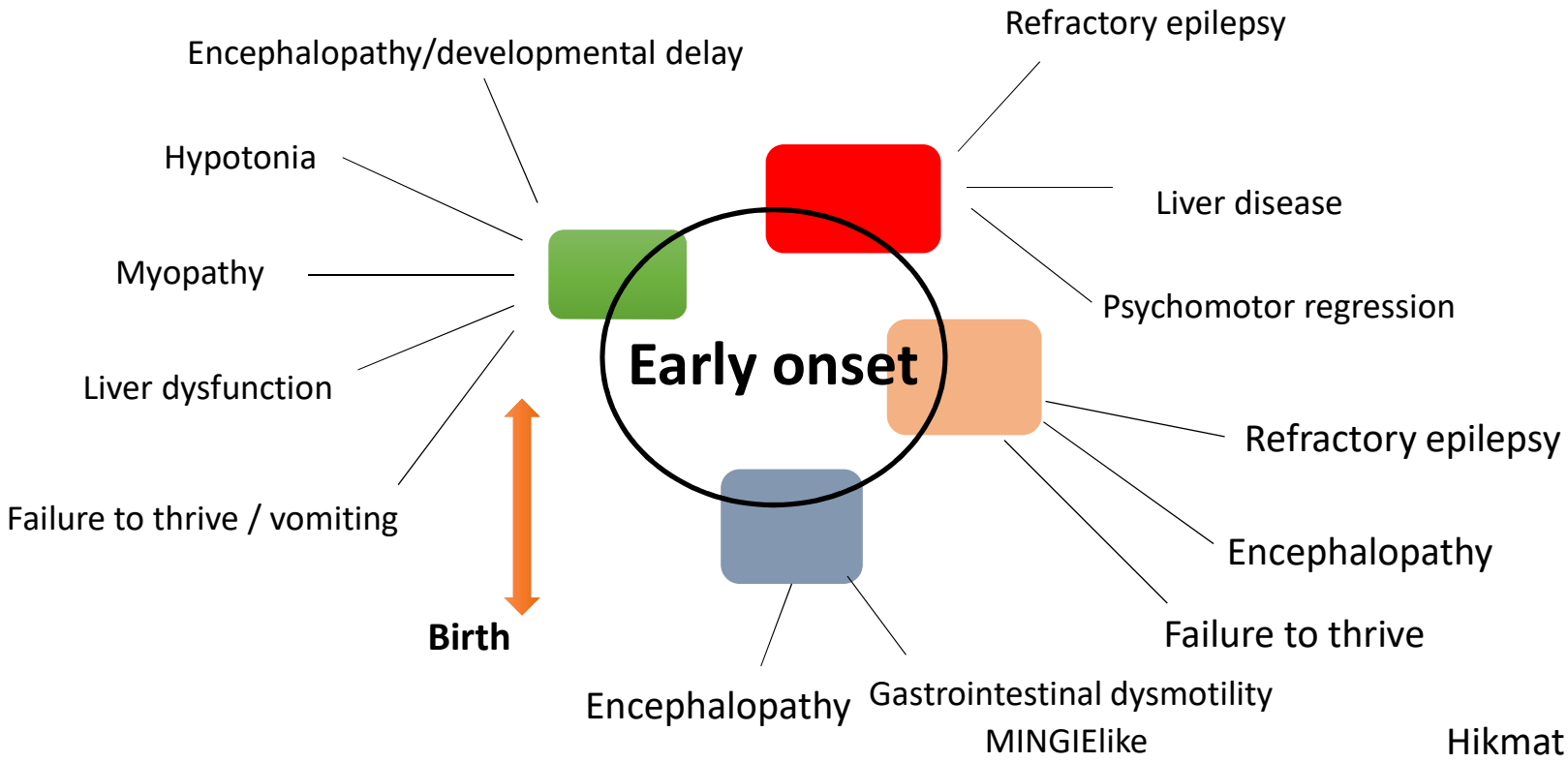


Fig. Hikmat

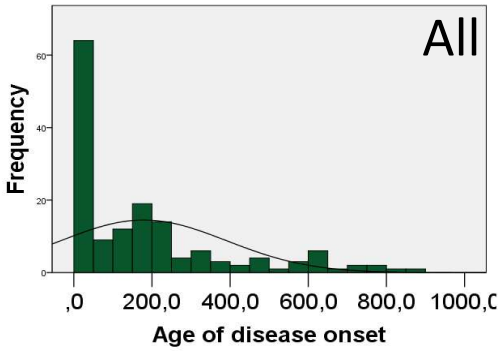
Patients with early onset disease may presented with or without epilepsy

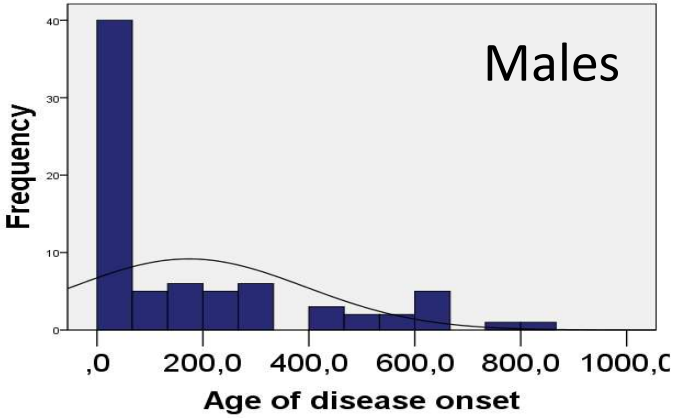


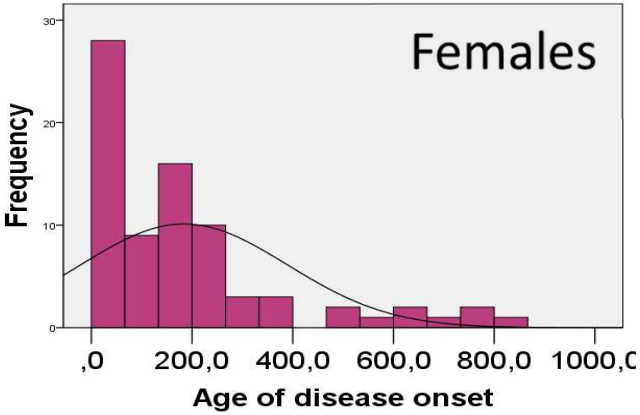
Hikmat et al GiM 2016

Gender, puberty and Pregnancy in POLG disease

Onset shows 2 peaks one early and the other in early teens (Data for ALL).
Appears that puberty in females is associated both with disease onset and increased disease activity. Males most at risk early.
Subsequent studies showed also that pregnancy may be associated with disease onset, seizure aggravation and status epilepticus








ANNALS of Clinical and Translational Neurology
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RESEARCH ARTICLE
The impact of gender, puberty, and pregnancy in patients with POLG disease
Omar Hikmat[1,2], Karin Naess[3,4], Martin Engvall[3,5], Claus Klingenberg[6,7], Magnhild Rasmussen[8,9], Chantal M. E. Tallaksen[10,11], Christian Samsonsen[12,13], Eylert Brodtkorb[12,13], Elsebet Ostergaard[14], Rene de Coo[15,16], Leticia Pias-Peleteiro[17], Pirjo Isohanni[18,19], Johanna Uusimaa[20,21], Niklas Darin[22], Shamima Rahman[23,24] & Laurence A. Bindoff[2,25]

Supportive Diagnostic investigations

- Haemtology, bl. gass**, Lactate**, pyruvate , CK, ASAT, ALAT, (NB GammaGT for liver invlolvement)
- **FGF-21 and GDF-15**
- **CSF: lactate , protein** , Pyruvate

- EEG , EMG , nerve conduction study.
- MRI / MRS

- Ragged Red Fibres (RRF).
- COX negative fibres./ SDH
- Electron microscope abnormal mitochondrial.
- Respiratory chain enzyme activities

Supportive Diagnostic investigations

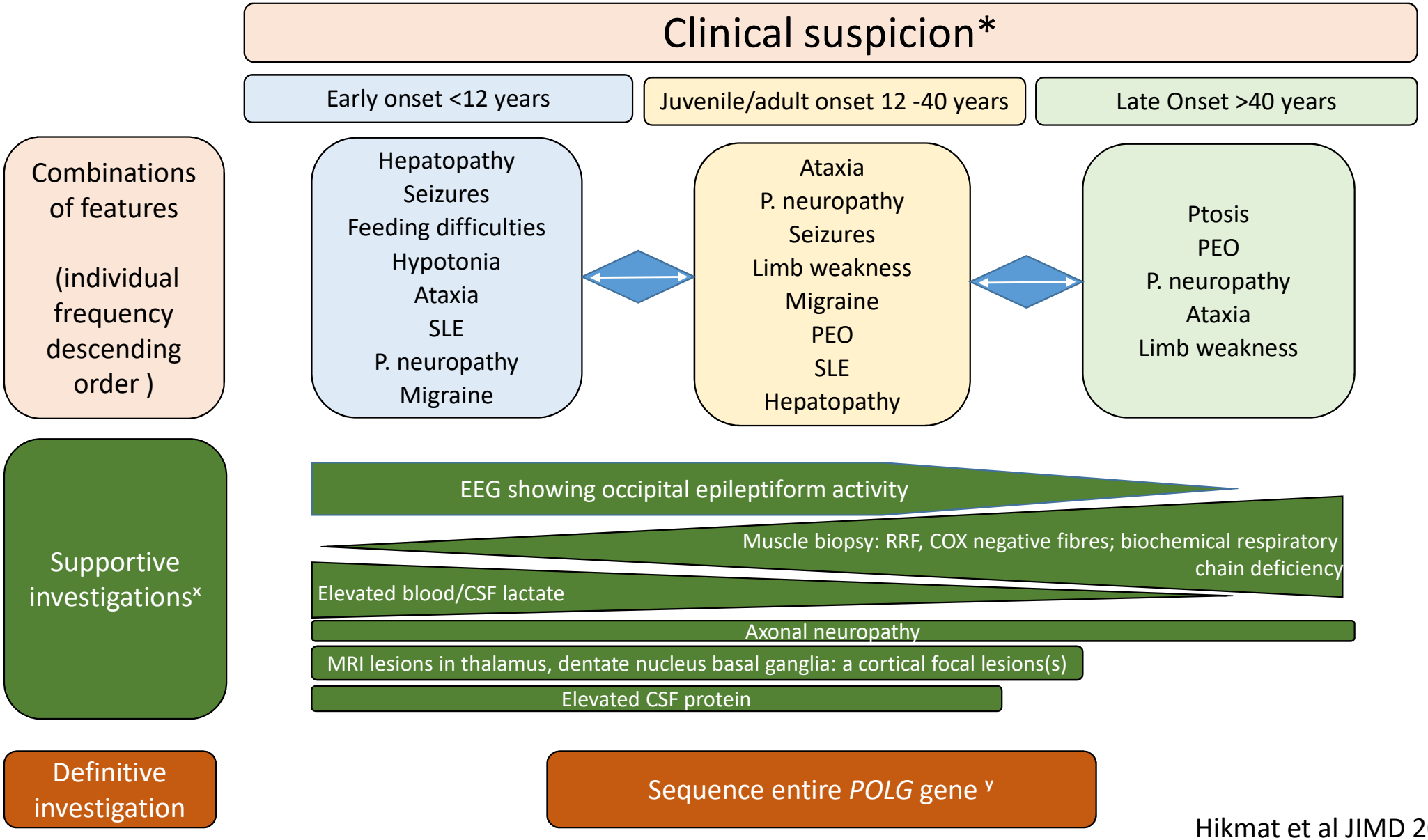
➢ **Neuro- imaging**:

Cortical focal lesions manifesting as T2/FLAIR hyperintensities affecting cortical and subcortical areas (not confined to vascular territories) and general cortical atrophy are the most frequently reported magnetic resonance imaging (MRI) abnormalities

➢ **EEG**:

- Ictal and inter-ictal occipital epileptic activity are highly suggestive for POLG disease, particularly in the early phase
- Rhythmic high amplitude with delta (RHADs) and focal slowing are frequently observed

Hikmat et al JIMD 2020



Hikmat et al JIMD 2020

Received: 14 August 2019 | Revised: 2 January 2020 | Accepted: 3 January 2020

DOI: 10.1002/jimd.12211

ORIGINAL ARTICLE

JIMD SSIEM WILEY

Simplifying the clinical classification of polymerase gamma (POLG) disease based on age of onset; studies using a cohort of 155 cases

Omar Hikmat[1,2] | Karin Naess[3,4] | Martin Engvall[3,5] | Claus Klingenberg[6,7] | Magnhild Rasmussen[8,9] | Chantal ME Tallaksen[10,11] | Eylert Brodtkorb[12,13] | Elsebet Ostergaard[14] | I. F. M de Coo[15,16] | Leticia Pias-Peleteiro[17] | Pirjo Isohanni[18,19] | Johanna Uusimaa[20,21,22] | Niklas Darin[23] | Shamima Rahman[24,25] | Laurence A. Bindoff[2,26]

Management

Symptomatic

Treatment of epilepsy

- Early recognition and immediate, aggressive seizure treatment are crucial to improving patient survival
- A majority of adult patients and approximately 90% of paediatric patients develop therapy resistant epilepsy
- Almost all require high dose polytherapy
- The most common seizure type in both in adults and paediatric patients is focal evolving to bilateral convulsive seizures

Bindoff & Engelsen Epilepsia 2012

Treatment of epilepsy

- Oxcarbazepine, carbamazepine, lacosamide and perampanel
- In combination with a benzodiazepine such as clobazam or clonazepam.
- (Lamotrigine), topiramate, levetiracetam
- Sodium valproate is absolutely contraindicated in patients with POLG disease due to the risk of liver disease

Hikmat et al IJMS 2017

Status epilepticus

- Should be treated quickly and aggressively
- Benzodiazepines, levetiracetam, phenytoin, phenobarbital
- Generalised anaesthesia using barbiturate (pentothal) or propofol to achieve Burst-suppression 48 hours
- Can try ketamine, isoflorane gas, cooling.
- Other things to consider
  - Ketogenic diet, Vagal Nerve Stimulation, Cannibidiol, Steroid
  - Nutritional supplements such as co-enzyme Q10, carnitine and vitamin cocktails appear to have no effect

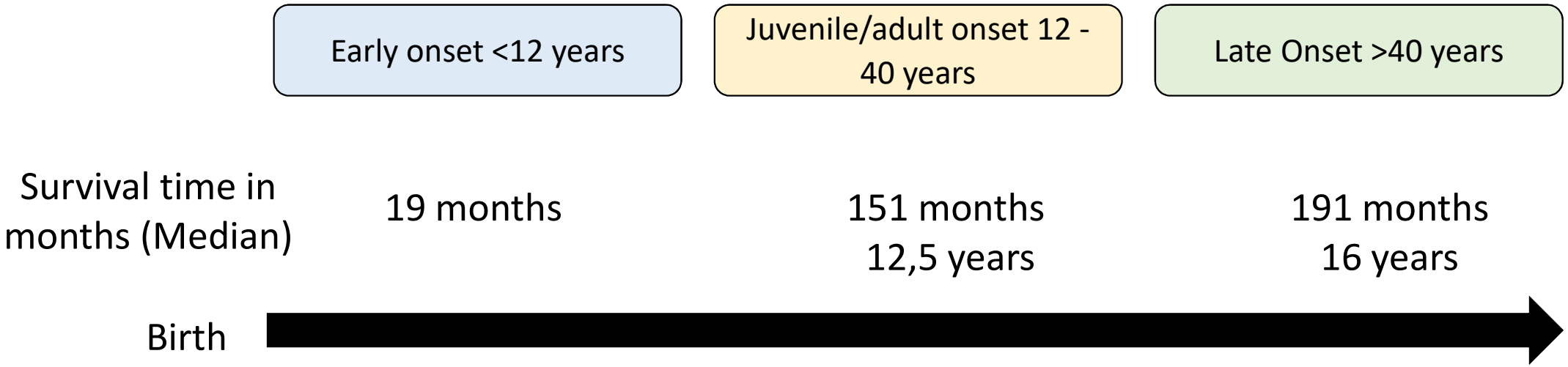
Hikmat et al IJMS 2017

- Our experience is consistent with the conclusion of a previously published Cochrane systemic review of those nutritional supplements that had been tested in randomised control trials none had any demonstrable clinical efficacy .
- Currently, there is no clear evidence showing the use of high dose coenzyme Q10, L-arginine and EPI-743 has any measurable effect on the epilepsy in patients with POLG disease.

Management
Symptomatic

- ***Gastrointestinal and nutritional****:*
  - *Constipation is a major problem:*
  - Gastroenterologist and dietician and the use of enteral nutrition via gastric tube/gastrostomy
- ***Liver dysfunction***:
  - Close monitoring of the liver function, Liver transplantation ?
- ***Movement disorder:***
  - L-dopa, benzodiazepine , botulinum toxin and oral/intrathecal baclofen
- ***Ophthalmological manifestations***:
  - ophthalmological evaluation, Surgery for ptosis ?

Prognosis depends on age of onset



Note: Early and juvenile onset disease is associated with worse prognosis

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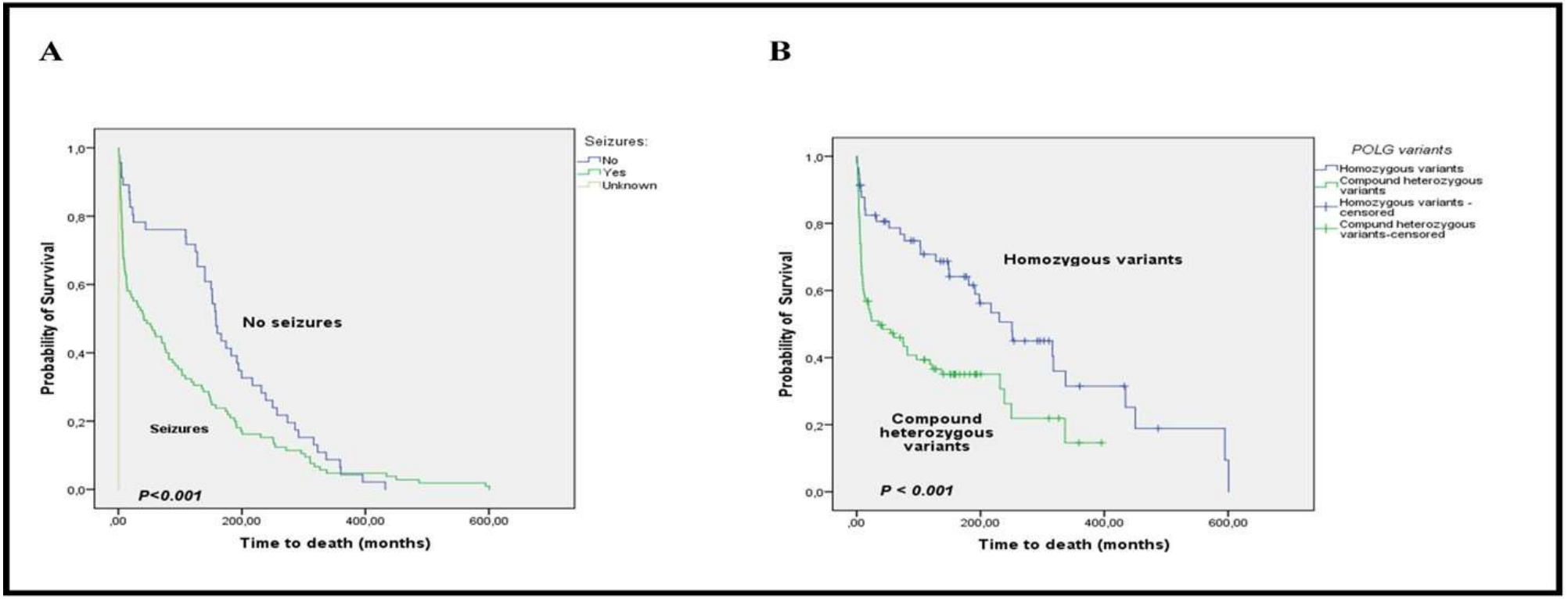
Prognosis

Epilepsy is significantly associated with worse prognosis

Patients with compound heterozygous *POLG* variants have a worse prognosis compared to those with homozygous variants



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National Norwegian POLG disease registry

www.polgregister.no

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Det er etablert et nasjonalt kvalitetsregister for pasienter med *POLG* sykdom
formålet er å kvalitetssikre diagnostikk og klinisk oppfølging og å øke kunnskap om sykdommene