VII Congresso ANEU: controversie in neurologia d'emergenza e urgenza

# Terapie innovative di malattie rare: porfiria

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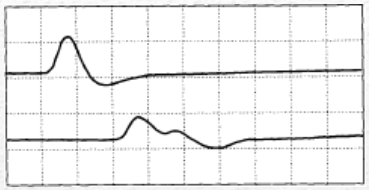
Associazione Neurologia Emergenza Urgenza

# Clinical case

**Day 1:** male, 31 years old, presents in ED on sunday night with persistent fever, progressive weakness and areflexia

CSF: cell 1/mmc, prot 154 mg/ml



Guillain-Barrè syndrome: starts IVIG

**Day 3:** abdominal pain, cramps, vomiting, tachycardia, hypertension

Radiology: negative
No surgical options

Anti-emetic, PPI, anti-hypertensive

**Day 4-5:** anxiety, hallucinations, generalized T-C seizure

Encephalitis, PRESS

Brain MRI: negative
EEG: negative

Neuroleptic, valproate

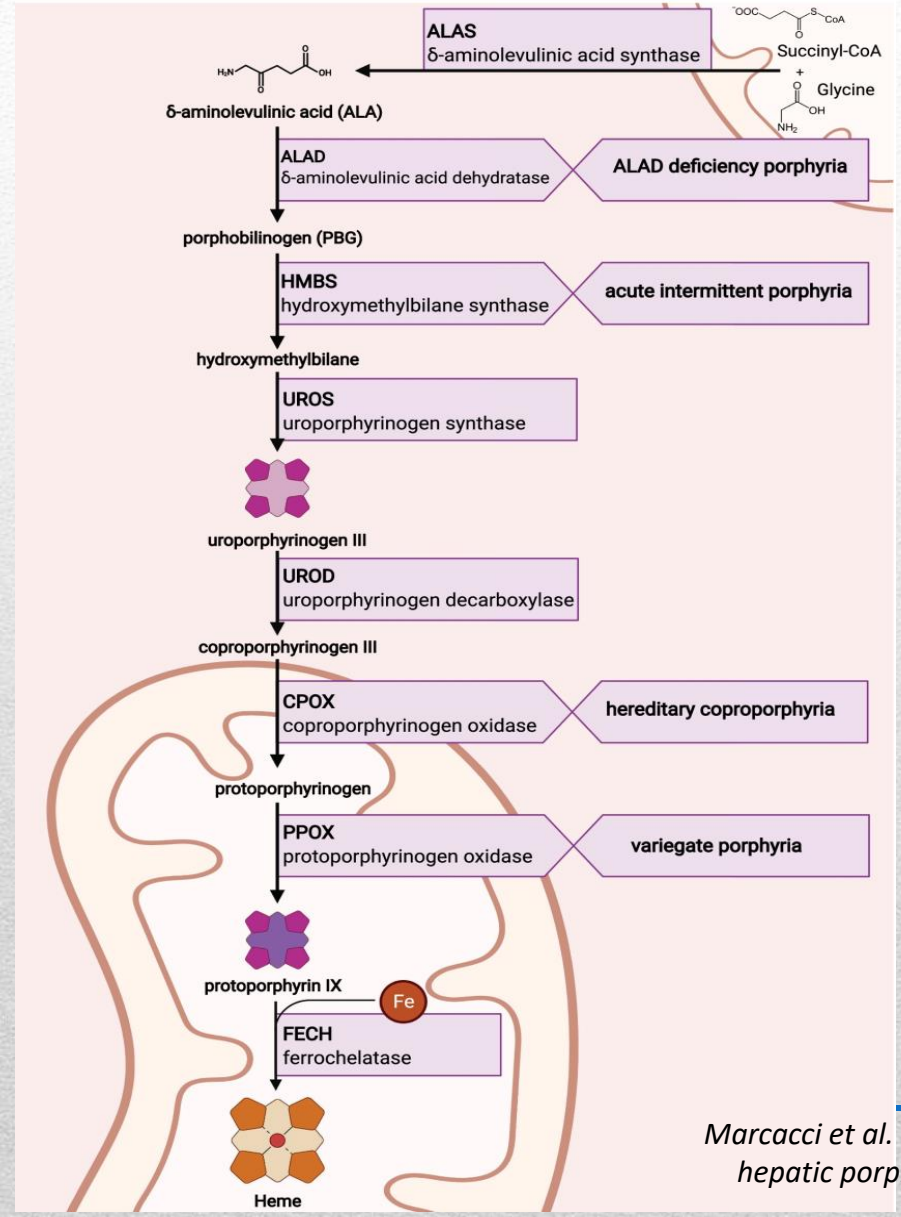
**Day 6-7:** sleepiness, coma

History of recurrent abdominal pain crisis

Dark urine with high ALA and PBG levels

diagnosis of **acute intermittent porphyria**

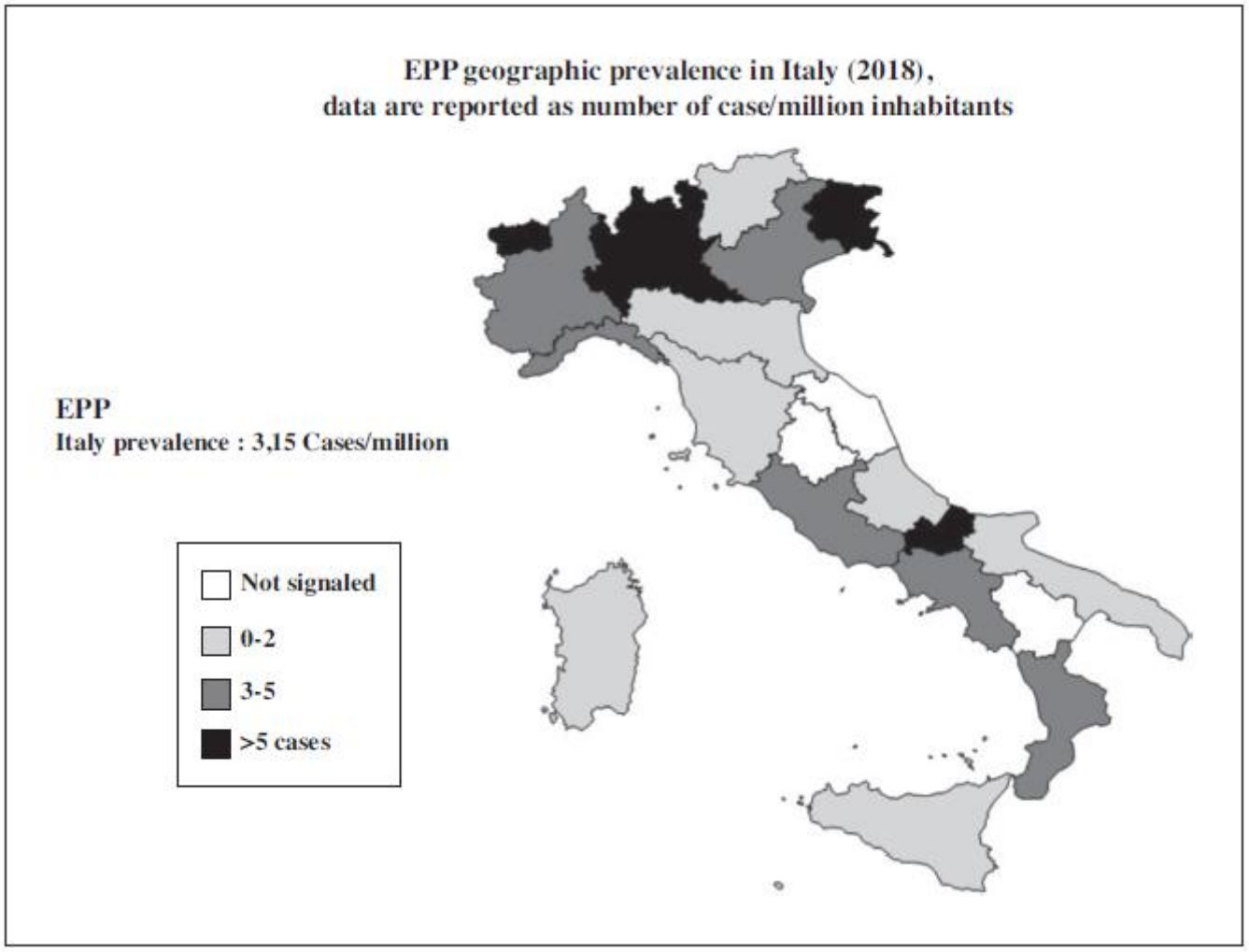
# Acute hepatic porphyrias




| Type | Allele and inheritance pattern [8] | Estimated prevalence of symptomatic patients (per million) [12] |
|---|---|---|
| AIP | HMBS[a] autosomal dominant | 5.9 |
| VP | PPOX autosomal dominant | 3.2 |
| HCP | CPOX autosomal dominant | 0.8 |
| ADP | ALAD autosomal recessive | Ultra-rare (< 10 documented cases) |

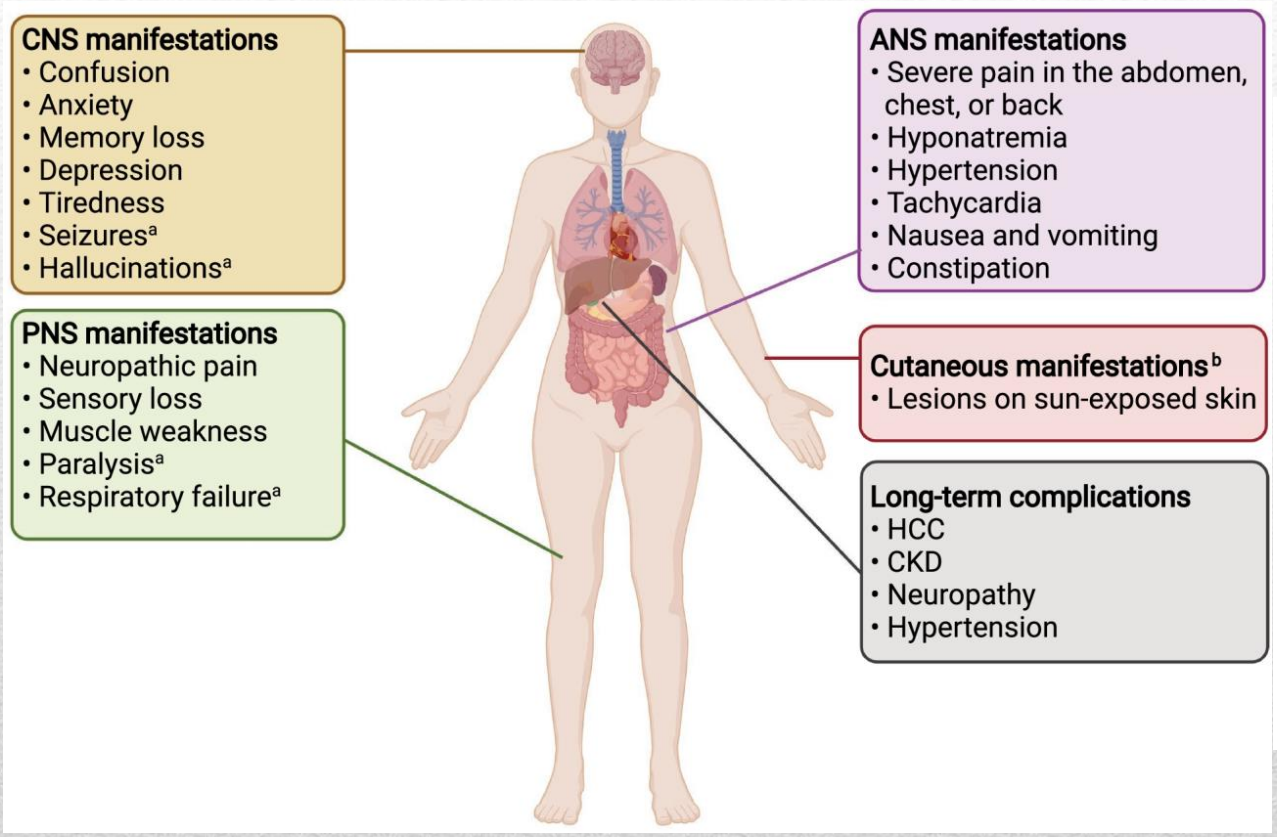
*Marcacci et al. Challenges in diagnosis and management of acute hepatic porphyrias. Orphanet Journal of Rare Diseases, 2022*

# Acute hepatic porphyrias




*Ventura et al. Clinical and molecular epidemiology of erythropoietic protoporphyria in Italy. Eur J Dermatol, 2020*

# Acute porphyric attack




| Signs/symptoms | % |
|---|---|
| Abdominal pain | 95–97 |
| Tachycardia | 65–80 |
| Urine darkening | 70–75 |
| Peripheral motor neuropathy | 40–60 |
| Constipation | 46–52 |
| Nausea, vomiting | 48–85 |
| Mental changes/psychosis | 10–40 |
| Hypertension (diastolic > 85 mmHg) | 38–64 |
| Hyponatriemia (<120 mEq/L) | 25–35 |
| Hypo/areflexia | 20–30 |
| Back pain | 20–30 |
| Sensory neuropathy | 20–28 |
| Hypotension | 15–22 |
| Seizures | 10–20 |
| Chest pain | 8–15 |
| Coma | 2–10 |

*Ventura et al. Recommendations for diagnosing acute porphyrias. Eur J Int Med, 2014*
*Puy et al. Porphyrias. Lancet, 2010*

# Acute porphyric attack

**Table 3**
Differential diagnosis of acute porphyric attack – common clinical conditions mimicked by an acute porphyric attack.

| |
|---|
| Surgical Conditions Associated with acute abdomen |
| (Peritonitis, appendicitis, acute cholecystitis, pancreatitis, intestinal occlusion, etc.) |
| **Dismetabolic/Disendocrine conditions** |
| Acute hypoadrenalism (Addisonian crisis) |
| Acute hypoparathyroidism and hypocalcemic crisis |
| Pheocromocytoma |
| **Neurolopsychiatric conditions** |
| Guillain–Barre' syndrome |
| Emicrania |
| Acute psychotic attack |
| Delirium |
| Acute panic attack |
| Epilepsy |
| Acute myopathies |
| **Cardiovascular conditions** |
| Hypertensive crisis |
| Tachyarrhythmia |
| **Haematological conditions** |
| Acute haemolytic crisis |
| Acute drepanocytic crisis |
| **Gastroenterological conditions** |
| Acute gastroenteritis with vomiting |

Severe, unexplained abdominal pain

*especially if present alongside any of the following*

- Pain in other areas
- Nausea, vomiting, constipation
- Hyponatremia, tachycardia, hypertension
- Muscle weakness
- Altered mental status
- Change in urine color

*Ventura et al. Recommendations for diagnosing acute porphyrias. Eur J Int Med, 2014*
*Lin et al. Nerve function and dysfunction in acute intermittent porphyria. Brain, 2008*

# Neuroporphyria

**central nervous system** (all AHPs)
mild symptoms:
headache, blurred vision,
insomnia, restlessness, anxiety

if severe: progressive neuropsychiatric symptoms, such as aberrant behavior, personality changes, depressive symptoms, hallucinations, mnestic deficits, altered consciousness, coma, seizures, status epilepticus

at any stage: hyponatremia

- Vascoconstriction, PRES, stroke
- EPC, absence, myoclonus

**Clinical trias:**

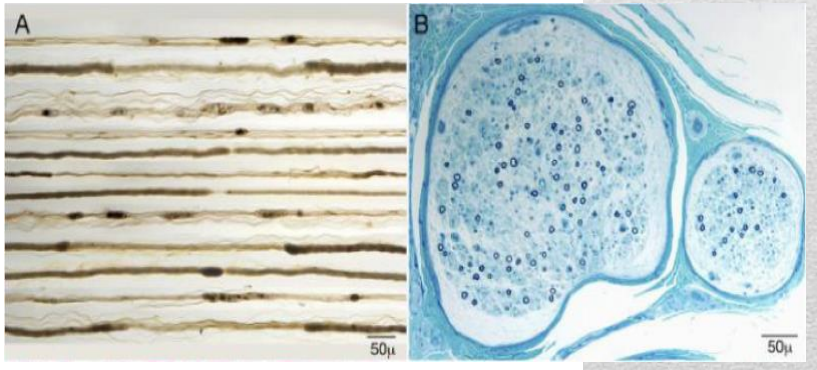
abdominal pain +
reddish/dark urine +
neuropsychiatric symptoms

**autonomic nervous system** (all AHPs)
excess sweating
raised body temperature

tachycardia,
orthostatic hypotension or labile hypertension

abdominal pain
nausea, vomiting
constipation or less frequent diarrhea
abdominal distension

urinary retention



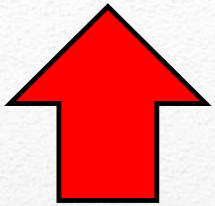

**peripheral nervous system** (all AHPs)
peripheral neuropathy
(mainly motor, mainly axonal)

sensory involvement:
mostly dysaesthesia and less commonly sensory loss

- Cranial neuropathy
- Rhabdomyolisis

*Ali et al. Porphyria: A rare differential diagnosis of polyradiculoneuropathy. J Neurol Sci, 2019*
*Gerischer et al. Acute porphyrias – A neurological perspective. Brain Behav 2021*

# Mechanisms of neural damage porphyrias



ALA

1. ALA may penetrate the blood-brain barrier, especially in region of greater permeability (hypotalamus, limbic area, neuromuscular junction)
2. ALA is structurally similar to GABA and Glutamate and may act as a partial agonist or antagonist of their receptors
3. ALA interacts with dioxovaleric acid increasing mitochondrial production of ROS

**CNS**

- Seizures
- NPS symptoms
- SIADH
- Motor pathways inhibition

**PNS**

- Neuronal metabolic damage
- Preferential motor neuron involvement (retrograde axonal transport?)

**ANS**

- Increased gut motility
- Neurovisceral pain

# Treatment

| Therapies downregulating ALAS1 | Dose and route of administration |
|---|---|
| IV heme | 3 to 4 mg/kg or 250 mg of heme daily in 100 mL human albumin (5%–20%) infused over 15–30 min in larger vein or central vein for 4–14 days |
| Glucose | IV (10% dextrose in sterile water or 0.45% saline) or oral 300 to 500 g/day of glucose |
| Discontinuation of porphyrinogenic drugs | American Porphyria Foundation website[117], the Norwegian Porphyria Centre[118] and a newer mobile app[119] have a full list of medications that can provoke a porphyria attack. |

Liver transplantation

| Class | Use only with extreme caution | Avoid |
|---|---|---|
| Anesthetic, sedative and hypnotic drugs | Ketamine | Ethomidate |
| | Lidocaine and Rupivacaine | Thiopentale |
| | Chlordiazepoxide and most of BZD (Flunitrazepam, alprazolam, nitrazepam, temazapam, triazolam) | Pentazocine |
| | | Barbiturates |
| Analgesic drugs and FANS | Diclofenac | Phenilbutazone |
| Antibiotics | Lincosamides | Cloramphenicole |
| | Metronidazole | Erythromycine |
| | Tetracyclines | Nitrofurantoine |
| | | Sulfonamides |
| | | Isoniazide |
| Diuretics | Indapamyde | |
| | Metholazone | |
| Anti-hypertensive and cardiologic drugs | Calcium-antagonists (dihydropyridine derivatives) | Methyldopa |
| | Hydralazine | |
| Lipid-lowering drugs | Fluvastatine, pravastatine e simvastatine | |
| Anti-ulcer and anti-emetic drugs | Esomeprazole andomeprazole | Dimenidrinate |
| Antidepressive drugs | Amitriptyline e Nortriptyline | |
| | Fluvoxamine, paroxetine e sertraline | |
| | Nefazodone and trazodone | |
| Antihepylectic drugs | Ethosuccimide | Valproic acid |
| | Felbamate | Carbamazepine |
| | Topiramate | Phenytoin |
| | | Phenobarbital |
| | | Primidone, meprobamate |
| | | Vigabatrine |
| Miscellanea | Clorpropamide | Tolbutamide |
| | Androgens (synthetic) | Ketoconazole and Miconazole |
| | Oral contraceptives | Gryseofulvin |
| | | Theophylline |

*Gandhi Mehta et al. Porphyric neuropathy. Muscle Nerve, 2021*
*Ventura et al. The acute porphyrias: a diagnostic and therapeutic challenge. Intern Emerg Med, 2009*

# Givosiran

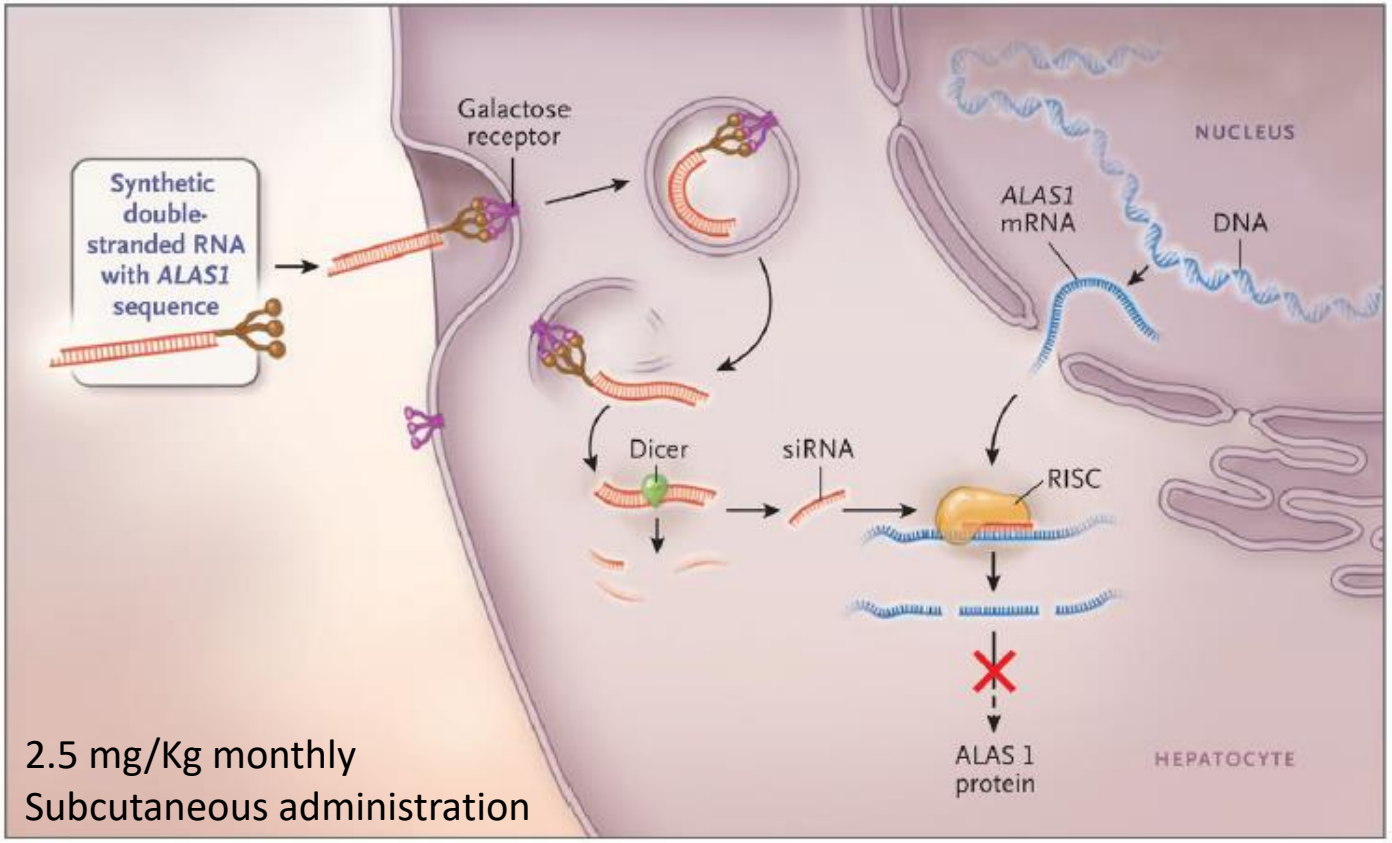
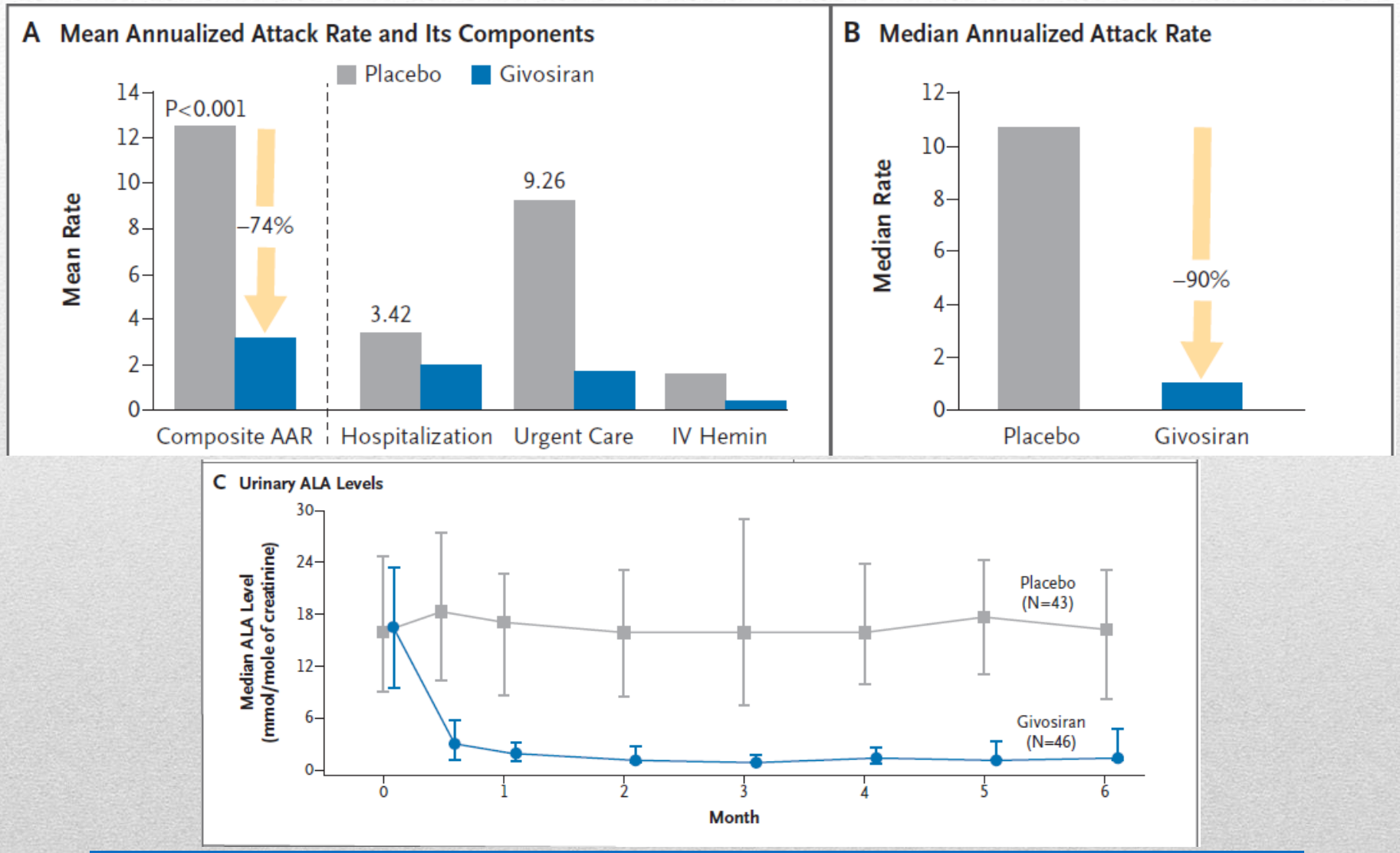



**FIG. 3.** The mechanism of siRNA therapy. Synthetic double-stranded RNA containing an ALAS-specific sequence is derivatized with N-acetylgalactosamine to target the asialoorosomucoid (galactose) receptor, which is expressed nearly exclusively on hepatocytes. Within the hepatocytes, the RNA is processed into approximately 20 base pair (bp) fragments by a cellular enzyme (dicer) and then separated into single strands. The strand that is complementary to *ALAS-1* (the guide strand) binds to cellular *ALAS-1* mRNA and enters the RNA-induced silencing complex, where the new double-stranded RNA is cleaved by a group of factors that include argonaute, a ribonuclease. The result is a reduction in the level of ALAS-1 protein and decreased production of ALA. Abbreviations: RISC, RNA-induced silencing complex. (From [5], used by permission of the authors and publisher.)

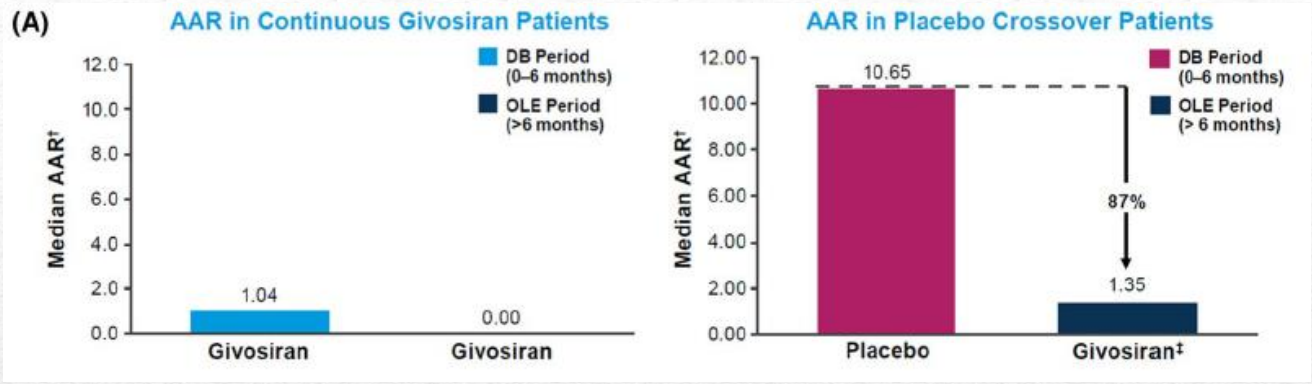
*Bissell DM et al. Porphyria. NEJM, 2017.*

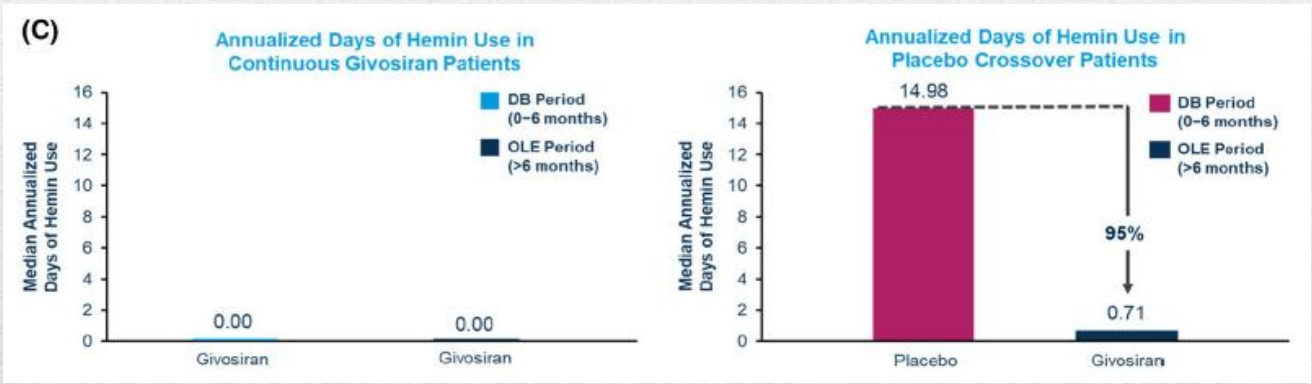
# Givosiran

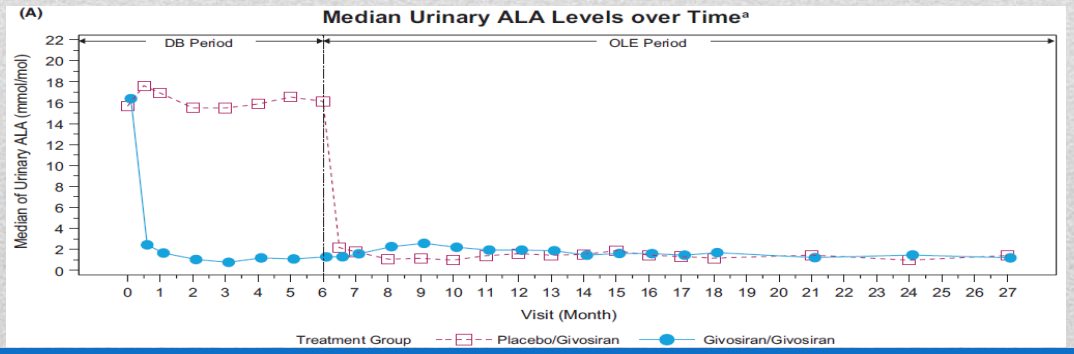



*Balwani et al. Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria. NEJM, 2020*

# Givosiran

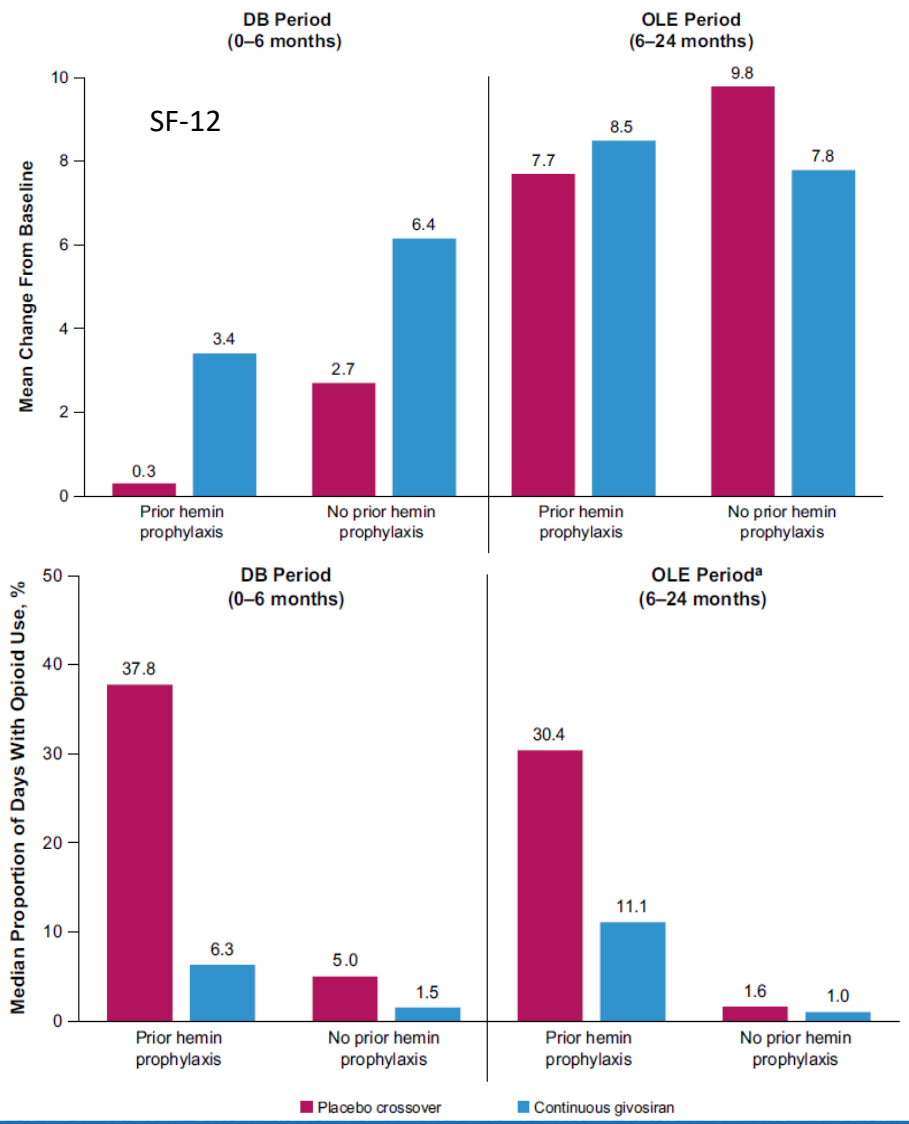



*Ventura et al. Efficacy and safety of givosiran for acute hepatic porphyria: 24-month interim analysis of the randomized phase 3 ENVISION study. Liver International, 2022*

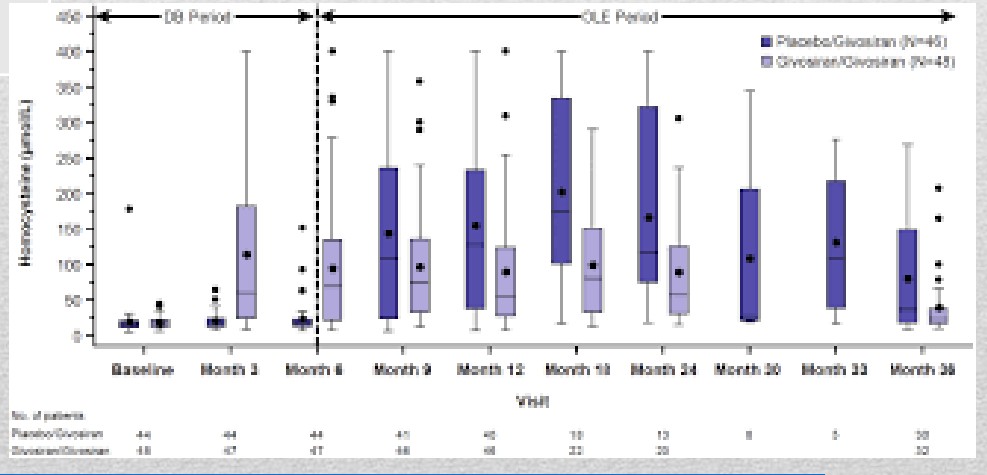
# Givosiran




*Wang et al.* Disease burden in patients with acute hepatic porphyria: experience from the phase 3 ENVISION study. *Orphanet Journal of Rare Diseases, 2022*

# Givosiran

| n (%) | Placebo crossover (n = 46) | Continuous givosiran (n = 48) | All givosiran (N = 94) |
|---|---|---|---|
| Any AE | 43 (94) | 47 (98) | 90 (96) |
| AEs occurring in ≥10% of patients | | | |
| Injection-site reactions[a] | 16 (35) | 19 (40) | 35 (37) |
| Nausea | 11 (24) | 21 (44) | 32 (34) |
| Fatigue | 10 (22) | 12 (25) | 22 (23) |
| Nasopharyngitis | 11 (24) | 11 (23) | 22 (23) |
| Headache | 7 (15) | 12 (25) | 19 (20) |
| Urinary tract infection | 8 (17) | 9 (19) | 17 (18) |
| Upper respiratory tract infection | 10 (22) | 6 (13) | 16 (17) |
| Vomiting | 8 (17) | 7 (15) | 15 (16) |
| Diarrhoea | 7 (15) | 7 (15) | 14 (15) |
| Abdominal pain | 6 (13) | 7 (15) | 13 (14) |
| Lipase increased | 6 (13) | 6 (13) | 12 (13) |
| Constipation | 4 (9) | 6 (13) | 10 (11) |
| Influenza | 5 (11) | 5 (10) | 10 (11) |
| AEs of interest | | | |
| Hepatic AEs[b] | 8 (17) | 9 (19) | 17 (18) |
| Renal AEs[c] | | | |
| Any event | 9 (20) | 12 (25) | 21 (22) |
| Increased serum creatinine or decreased eGFR[d] | 8 (19) | 13 (27) | 21 (22) |
| Any serious AE | 13 (28) | 15 (31) | 28 (30) |
| Any severe AE | 14 (30) | 13 (27) | 27 (29) |
| Any AE leading to treatment discontinuation | 2 (4) | 1 (2) | 3 (3) |
| Any AE leading to study withdrawal | 2 (4) | 1 (2) | 3 (3) |
| Death | 0 | 0 | 0 |




*Ventura et al. Hyperhomocysteinemia in acute hepatic porphyria (AHP) and implications for treatment with givosiran. Expert Rev Gastroenterol Hepatol, 2022*

# What about porphyric neuropathy?

| | Placebo crossover (n = 46) | Continuous givosiran (n = 48) | All givosiran (N = 94) |
|---|---|---|---|
| Neuropathy, n (%) | 16 (35) | 20 (42) | 36 (38) |
| Sensory | 8 (17) | 10 (21) | 18 (19) |
| Motor | 8 (17) | 13 (27) | 21 (22) |
| Autonomic | 3 (7) | 0 | 3 (3) |

**Case study:** male, 12 years old

At age 5: first acute porphyric attack with diagnosis of acute intermittent porphyria with double heterozigous mutation of PBG deaminase gene. Acute 4-limbs weakness, resolved.

Multiple acute porphyric attacks, refractory to chronic hemin infusions.

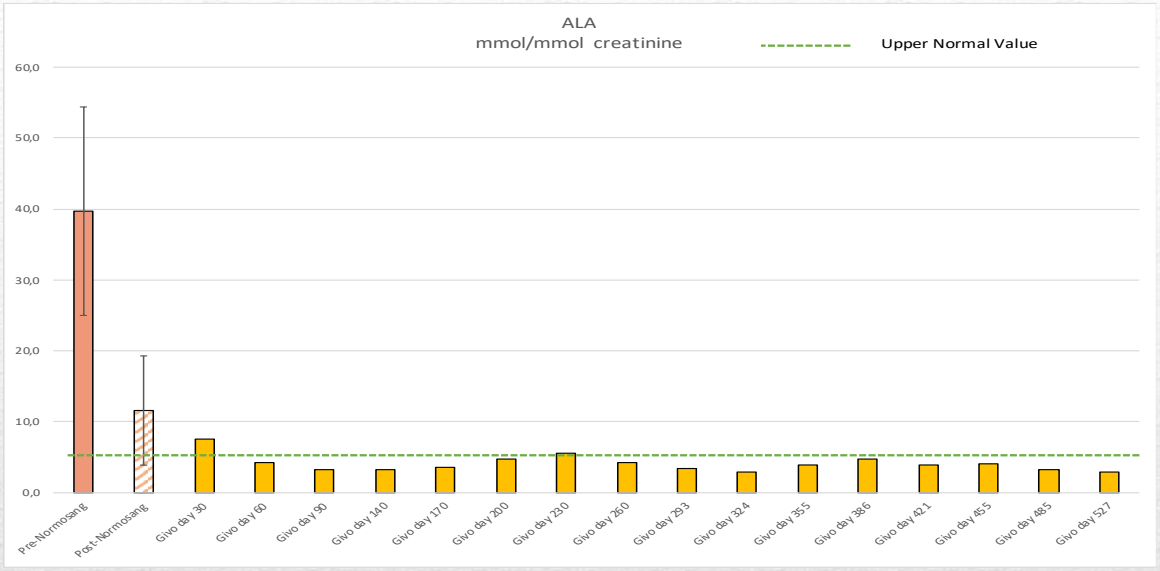
Since age 6: diffuse distal limbs weakness with severe bilateral foot drop, chronic pain and mild hand-feet paresthesia. Pes cavus with Achille's tendon retraction. Wheelchair-bound.

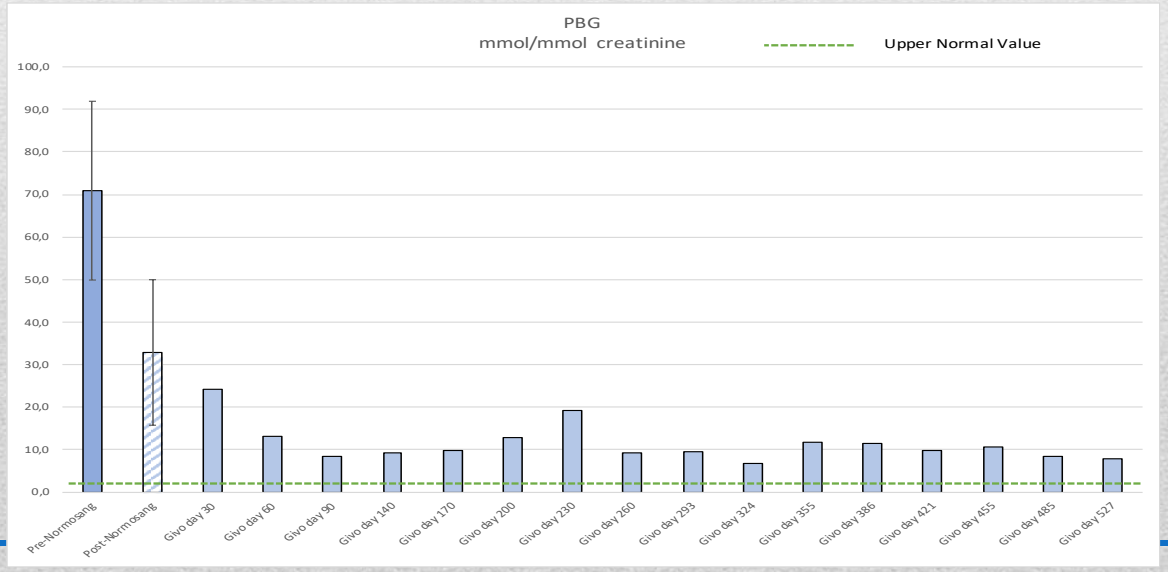
ENG: chronic axonal simmetric motor polyneuropathy (diffuse reduction of cMAP amplitude, in particular for fibular, median and radial nerves). No conduction failures.

Other causes of neuropathy were excluded (immune, metabolic, genetic). Normal CSF.

Started Givosiran 2,5 mg/Kg every month (age 12).

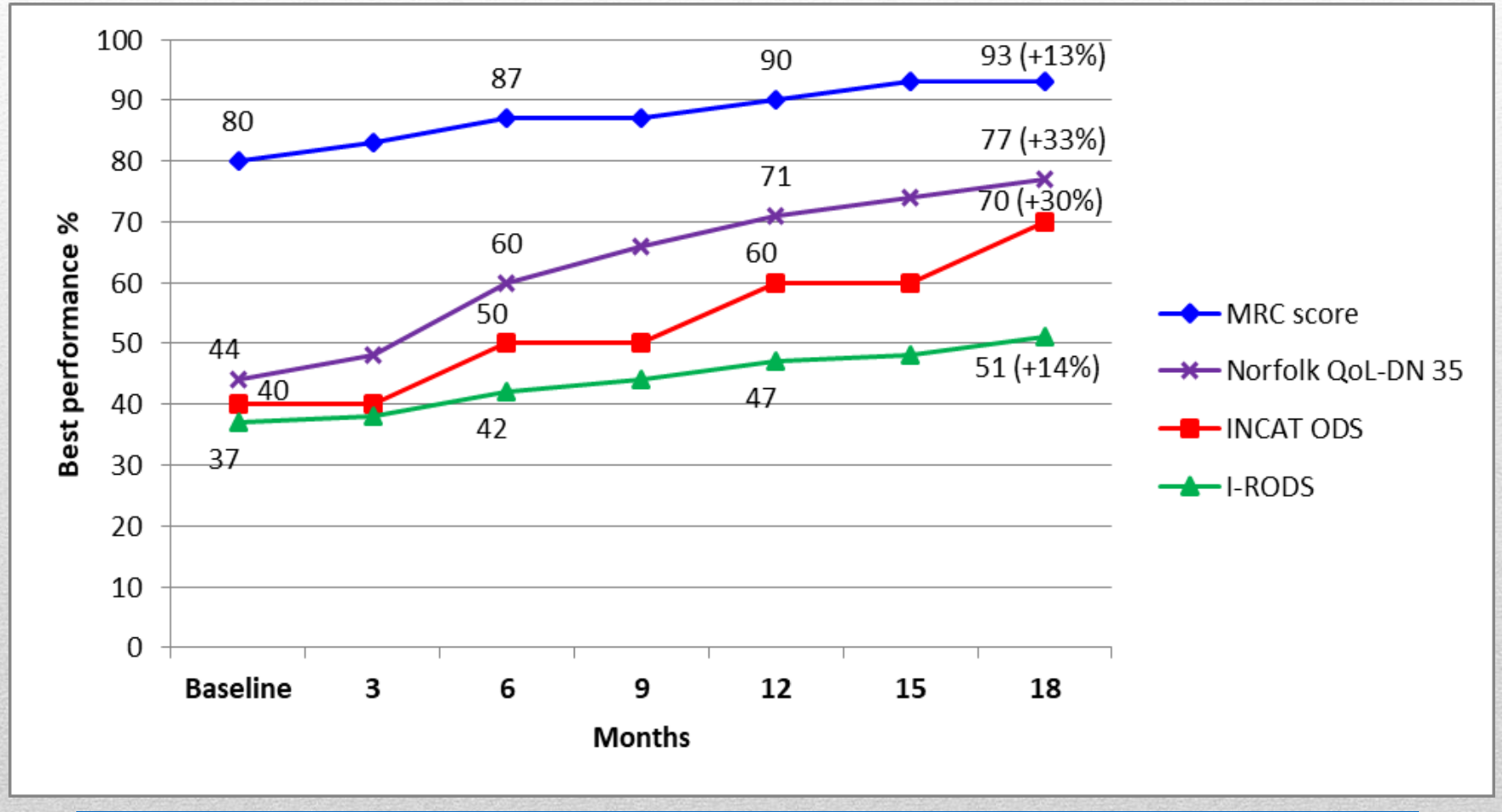
# ALA and PBG trends



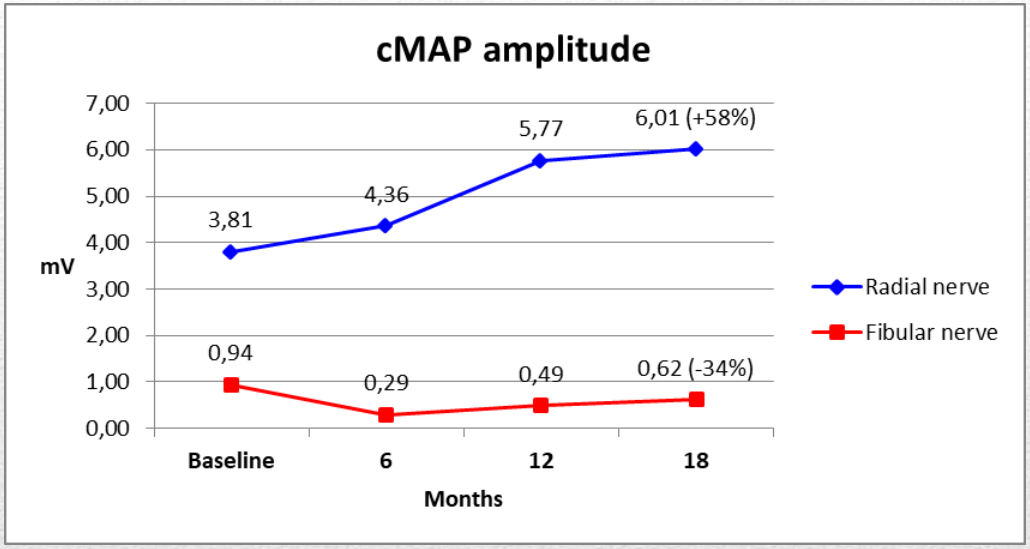



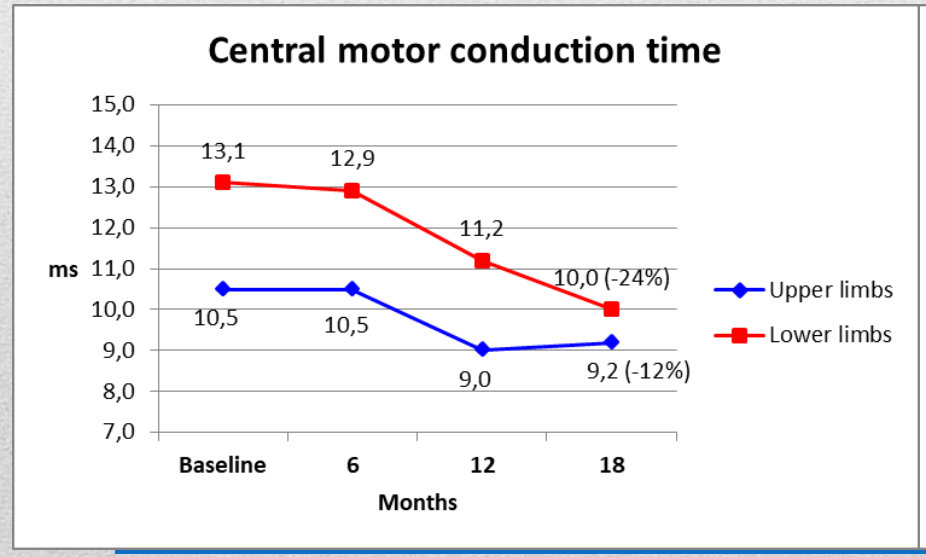
# Clinical outcome measures

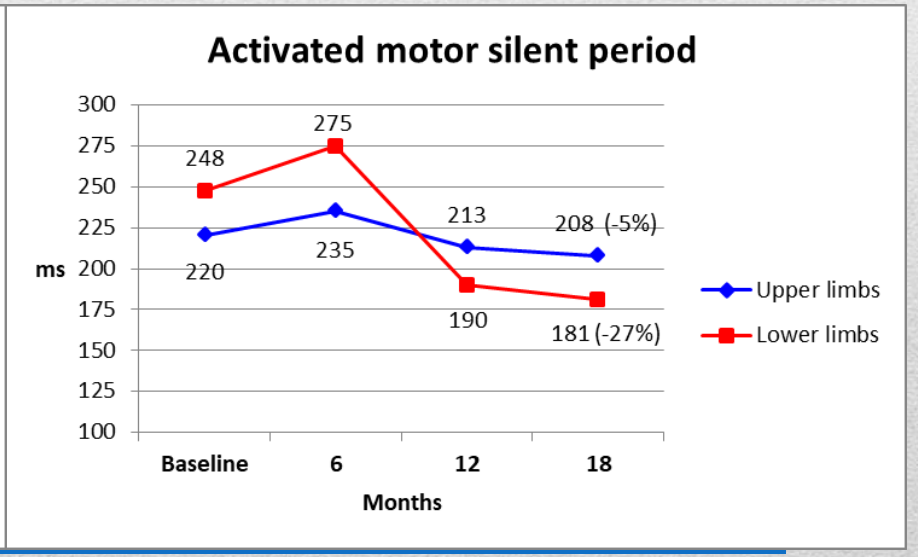
- Patient had no acute porphyric attack during Givosiran treatment
- Chronic Hemin infusions were stopped



# Neurophysiological outcome measures

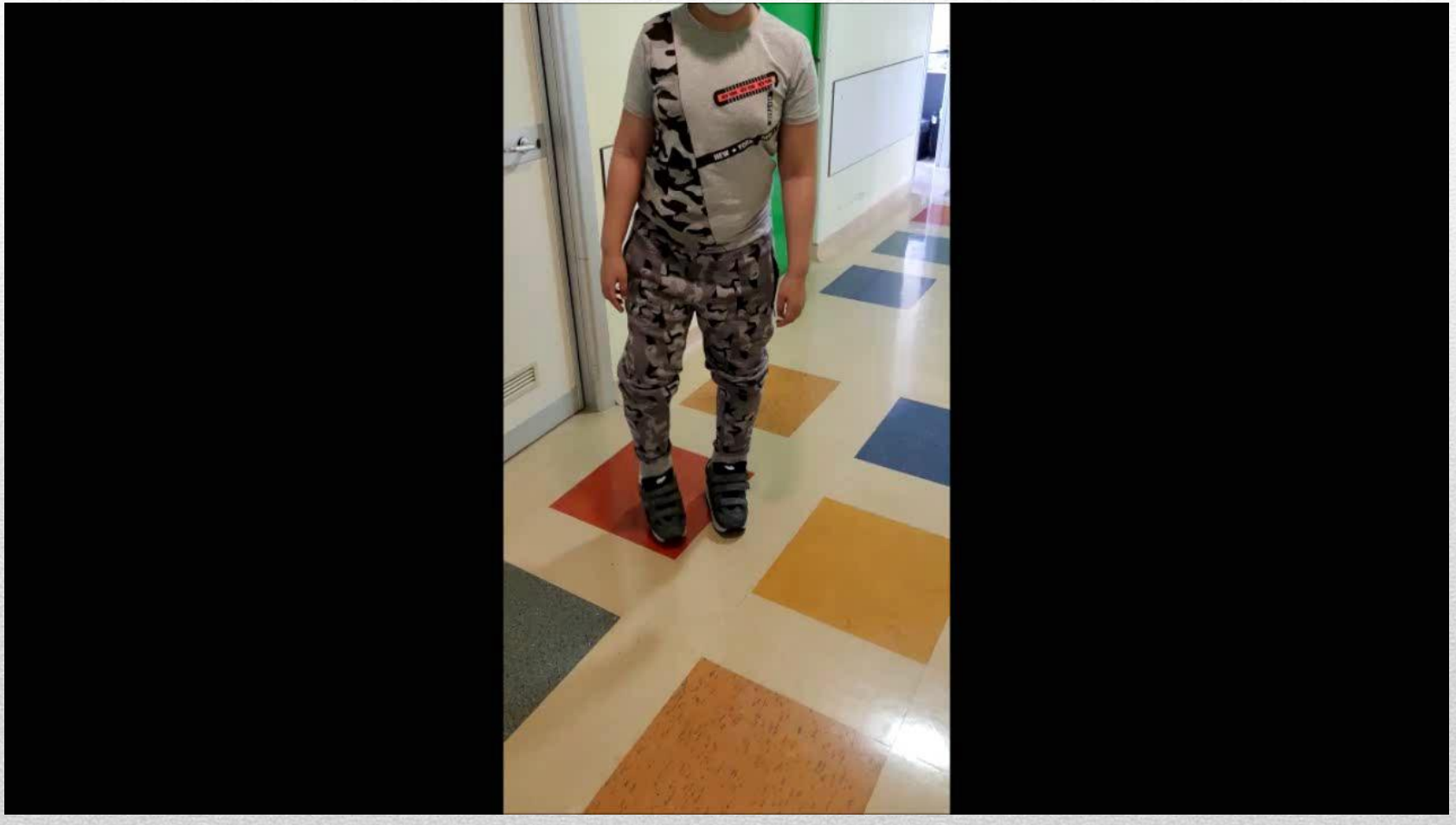


# Evident improvement

- The patient has been wheelchair-bound for seven years
- After 8 months of Givosiran treatment he was able to walk without assistance



# Conclusions

Acute porphyric attack is a medical emergency that must be take into consideration for differential diagnosis of different neurologic and psychiatric conditions

Acute porphyric attack is potentially life-threatening and may cause permanent sequelae, but it can be easily treated if diagnosed in time

Givosiran is safe and effective in preventing acute porphyric attacks: it must be promptly started in patients with a new diagnosis of acute hepatic porphyria

Givosiran may have a potential role for the treatment of neurological manifestations of porphyria: further studies are ongoing to demonstrate that

# Terapie innovative di malattie rare: porfiria

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- ***Prof. Paolo Ventura, Dr. Matteo Marcacci, Dr. Andrea Ricci**: UOC Medicina interna AOU Modena, Dipartimento di Scienze Mediche e Chirurgiche Università di Modena e Reggio Emilia*

*Roma, 30 settembre 2022*