Non-ketotic hyperglycinemia

(Glycine encephalopathy)

دکترعبدالحسین نیک روش

گروه غدد ومتابولیسم کودکان دانشگاه علوم پزشکی بوشهر

case

- Our patient began to display neurological symptoms when she was 10 days old: hypotonia, lethargy, apnoea, and myoclonic seizures.she was intubated for near one month..
- No fever/ biochemical abnormalities /sepsis/ammonia & lactate /brain anomaly in ct scan
- Her screening metabolic test was normal
- Suspicion of West syndrome was confirmed by EEG findings (burst-suppression during the first weeks of life, progressing to hypsarrhythmia a month after birth) ..brain lactate was normal
- The patient was initially treated with valproate and gabapentin , with no improvement.

Neonatal Epileptic Encephalopathy

- ISOD/Mb cofactor deficiency
- Glycine Encephalopathy
- Urea Cycle disorders
- Mitochondrial Disease
- Organic acidemias
- Zellweger Syndrome
- Pyridoxine-dependent epilepsy

Although the large range of metabolic etiologies, only cases of the most frequent IMD related Neonatal Epileptic encephalopathy and with MRI slightly suggestive pattern will be presented.

- The second metabolic test showed an increase in glycine in serum amino acids. . While urine organic acids and serum acylcarnitines were again normal
- Laboratory analysis revealed a glycine level of 920 µM in the serum and 229µM in the CSF and CSF/serum ratio, 0.25 [normal range, <0.12]
- After stopping Valpreat, my blood was checked again and the number 745µM (nl<426) was obtained
- The patient was diagnosed with classic neonatal NKH.
- He was treated with sodium benzoate, dextromethorphan, and anticonvulsant drugs. After about 1 year, the seizures not decreased and but blood glycine level is normal and in terms of development, it has a clear developmental delay..

GLDC ..exon21
c.2458A>G
p.M820V

Gene & transcript	Variant	Chromosomal location	Associated disease	OMIM	Zygosity[a]	CADD Score[b]	dbSNP rsID[c]	ACMG Classification[d]	Inheritance[e]
GLDC NM_000170.3	Exon21 c.2458A>G p.M820V	chr9-6550914 T>C	Glycine encephalopathy	605899	Hom	23.9	rs781682244	VUS	AR
CCDC47 NM_020198.3	Exon11 c.1188C>G p.F396L	chr17-61829695 G>C	Trichohepatoneurodevelopmental syndrome	618268	Hom	22.2	-	VUS	AR

هو الشافی

مرکز جامع ژنتیک پزشکی جنوب کشور (شهید سلطانی)
Comprehensive Medical Genetics Center
BS EN ISO 9001:2015

شماره : .....
تاریخ : ۱۴۰۱/۶/۳۰
پیوست : .....

Proband: اصغر نجاتی (حسین) **Molecular Lab No:** 7322

Requested Assay: Target following mutation analysis:

Gene	Transcript	Variation
GLDC	NM_000170.3	c.2458A>G, p.M820V
CCDC47	NM_020198.3	c.1188C>G, p.F396L

Sample: Genomic DNA isolated from EDTA blood
Requested by: دکتر مریم تقدیری
Date Sample Received: 12.4.1401
Methods: Sequencing

Results:

Gene	Chromosome	Variation	Genotype	Mode of Inheritance
GLDC	9	c.2458A>G, p.M820V	**Heterozygous**	AR
CCDC47	17	c.1188C>G, p.F396L	**Heterozygous**	AR

Variation analysis:

Gene	Variation	Sift	Mutation taster	Polyphen	Provean	ACMG	Associated disease
GLDC	c.2458A>G, p.M820V	Damaging	Deleterious	Probably damaging	Damaging	Pathogenic/ VUS	Glycine encephalopathy
CCDC47	c.1188C>G, p.F396L	Tolerated	Benign	Benign	Damaging	VUS	Trichohepatoneurodevelopmental syndrome

Recommendation: Proband and his family need a proper consultation.
Limitations: Large deletions, duplications, mutations in regulatory regions and not requested regions were not investigated.

Additional Comments: It is of utmost importance for all clinicians involved in the care of families requesting molecular genetics diagnostic tests and the families themselves to be aware of the risk of errors in DNA analysis. Incorrect analysis may result from 1) incorrect data and clinical diagnosis 2) incomplete family studies and history 3) mix-up of DNA samples and mislabeling 4) rare molecular events5) new or spontaneous mutations 6) paternity problems, adaptation, IVF, egg donor, bone marrow transplantation, recent blood product transfusion 7) maternal DNA contamination of CVS or amniotic fluid samples 8) technical errors. The risk of errors from various reasons mentioned above and several others is about 0.5%, while the chance of technical errors of all types is estimated to be around 0.5%. The risk of errors due to DNA recombination in diagnosis is approximately 0.3%. We take no responsibility about patient identity and possible mislabeling of the DNA samples. Any feedback from our colleagues in the clinical field would be most welcomed. Comments can be given in writing or by e-mail to: m.entezam@gmail.com
It should be noted that the classification of the above mentioned variant is based on current findings and there is a possibility to change in the future. Co-segregation of the above mentioned variant is highly recommended for the other affected members of the family and this evidence may help to reclassification of reported variant.

Dr. Mona Entezam
Medical Geneticist
Comprehensive Medical Genetics Center,
Shiraz University of Medical Sciences,
Shiraz, Iran

مرکز جامع ژنتیک پزشکی جنوب کشور
دکتر مونا انتظام
متخصص ژنتیک پزشکی - استادیار تمام وقت
دانشگاه علوم پزشکی و خدمات بهداشتی درمانی شیراز ۳۸۳۴۱

شیراز : خیابان قصردشت/ جنب پایگاه منطقه ای اورژانس فارس/ نبش کوچه ۹۳ / مرکز جامع ژنتیک پزشکی جنوب کشور (شهید سلطانی)
تلفن : ۲۲ -۳۶۳۰۳۴۴۱ - ۰۷۱
www.shirazgen.ir info@shirazgen.ir

هو الشافی

مرکز جامع ژنتیک پزشکی جنوب کشور (شهید سلطانی)
Comprehensive Medical Genetics Center
BS EN ISO 9001:2015

شماره : .....
تاریخ : ۱۴۰۱/۶/۳۰
پیوست : .....

Proband: فائزه نجاتی (محمد) **Molecular Lab No:** 7322

Requested Assay: Target following mutation analysis:

Gene	Transcript	Variation
GLDC	NM_000170.3	c.2458A>G, p.M820V
CCDC47	NM_020198.3	c.1188C>G, p.F396L

Sample: Genomic DNA isolated from EDTA blood
Requested by: دکتر مریم تقدیری
Date Sample Received: 12.4.1401
Methods: Sequencing

Results:

Gene	Chromosome	Variation	Genotype	Mode of Inheritance
GLDC	9	c.2458A>G, p.M820V	**Heterozygous**	AR
CCDC47	17	c.1188C>G, p.F396L	**Heterozygous**	AR

Variation analysis:

Gene	Variation	Sift	Mutation taster	Polyphen	Provean	ACMG	Associated disease
GLDC	c.2458A>G, p.M820V	Damaging	Deleterious	Probably damaging	Damaging	Pathogenic/ VUS	Glycine encephalopathy
CCDC47	c.1188C>G, p.F396L	Tolerated	Benign	Benign	Damaging	VUS	Trichohepatoneurodevelopmental syndrome

Recommendation: Proband and his family need a proper consultation.
Limitations: Large deletions, duplications, mutations in regulatory regions and not requested regions were not investigated.

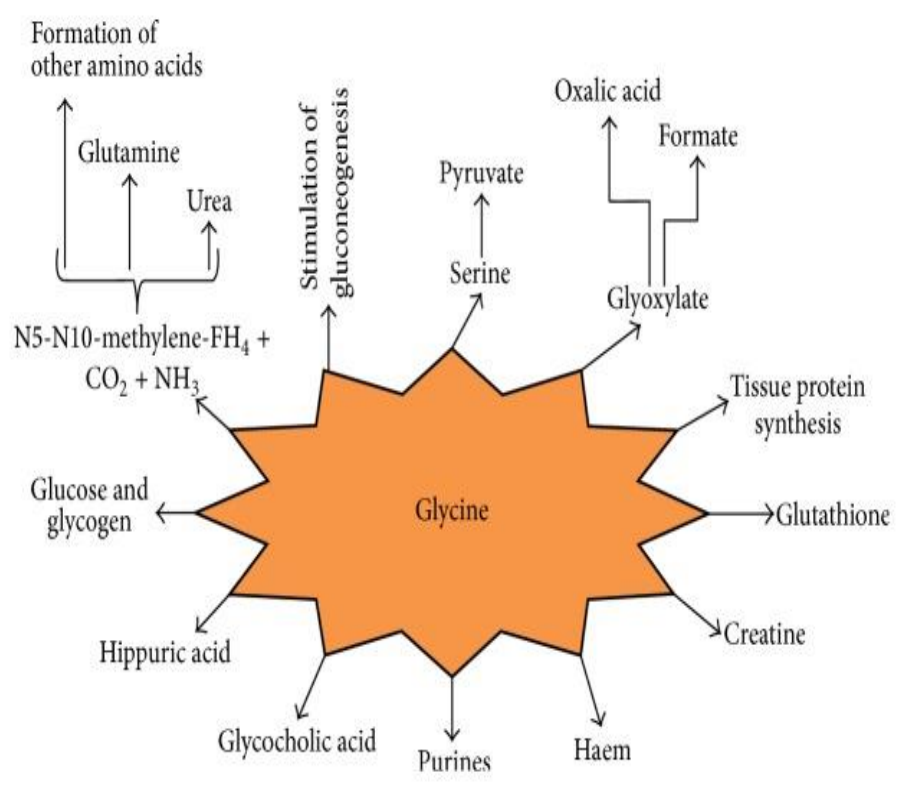
Additional Comments: It is of utmost importance for all clinicians involved in the care of families requesting molecular genetics diagnostic tests and the families themselves to be aware of the risk of errors in DNA analysis. Incorrect analysis may result from 1) incorrect data and clinical diagnosis 2) incomplete family studies and history 3) mix-up of DNA samples and mislabeling 4) rare molecular events5) new or spontaneous mutations 6) paternity problems, adaptation, IVF, egg donor, bone marrow transplantation, recent blood product transfusion 7) maternal DNA contamination of CVS or amniotic fluid samples 8) technical errors. The risk of errors from various reasons mentioned above and several others is about 0.5%, while the chance of technical errors of all types is estimated to be around 0.5%. The risk of errors due to DNA recombination in diagnosis is approximately 0.3%. We take no responsibility about patient identity and possible mislabeling of the DNA samples. Any feedback from our colleagues in the clinical field would be most welcomed. Comments can be given in writing or by e-mail to: m.entezam@gmail.com
It should be noted that the classification of the above mentioned variant is based on current findings and there is a possibility to change in the future. Co-segregation of the above mentioned variant is highly recommended for the other affected members of the family and this evidence may help to reclassification of reported variant.

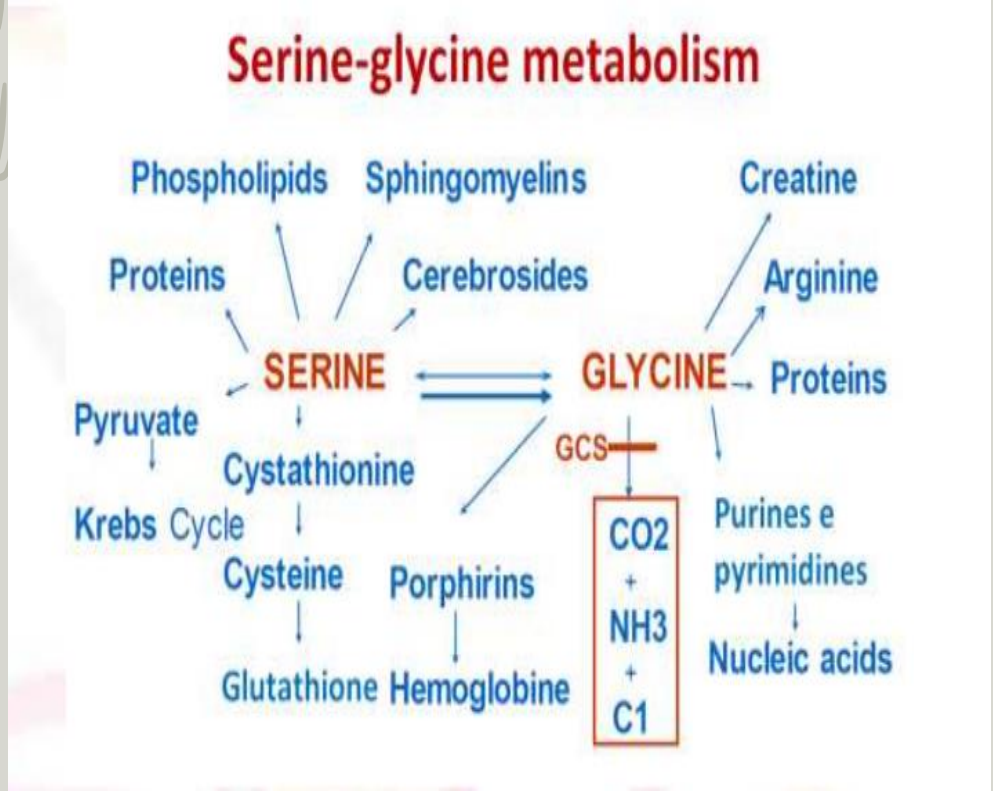
Dr. Mona Entezam
Medical Geneticist
Comprehensive Medical Genetics Center,
Shiraz University of Medical Sciences,
Shiraz, Iran

مرکز جامع ژنتیک پزشکی جنوب کشور
دکتر مونا انتظام
متخصص ژنتیک پزشکی - استادیار تمام وقت
دانشگاه علوم پزشکی و خدمات بهداشتی درمانی شیراز ۳۸۳۴۱

شیراز : خیابان قصردشت/ جنب پایگاه منطقه ای اورژانس فارس/ نبش کوچه ۹۳ / مرکز جامع ژنتیک پزشکی جنوب کشور (شهید سلطانی)
تلفن : ۲۲ -۳۶۳۰۳۴۴۱ - ۰۷۱
www.shirazgen.ir info@shirazgen.ir

WHAT IS GLYCINE?

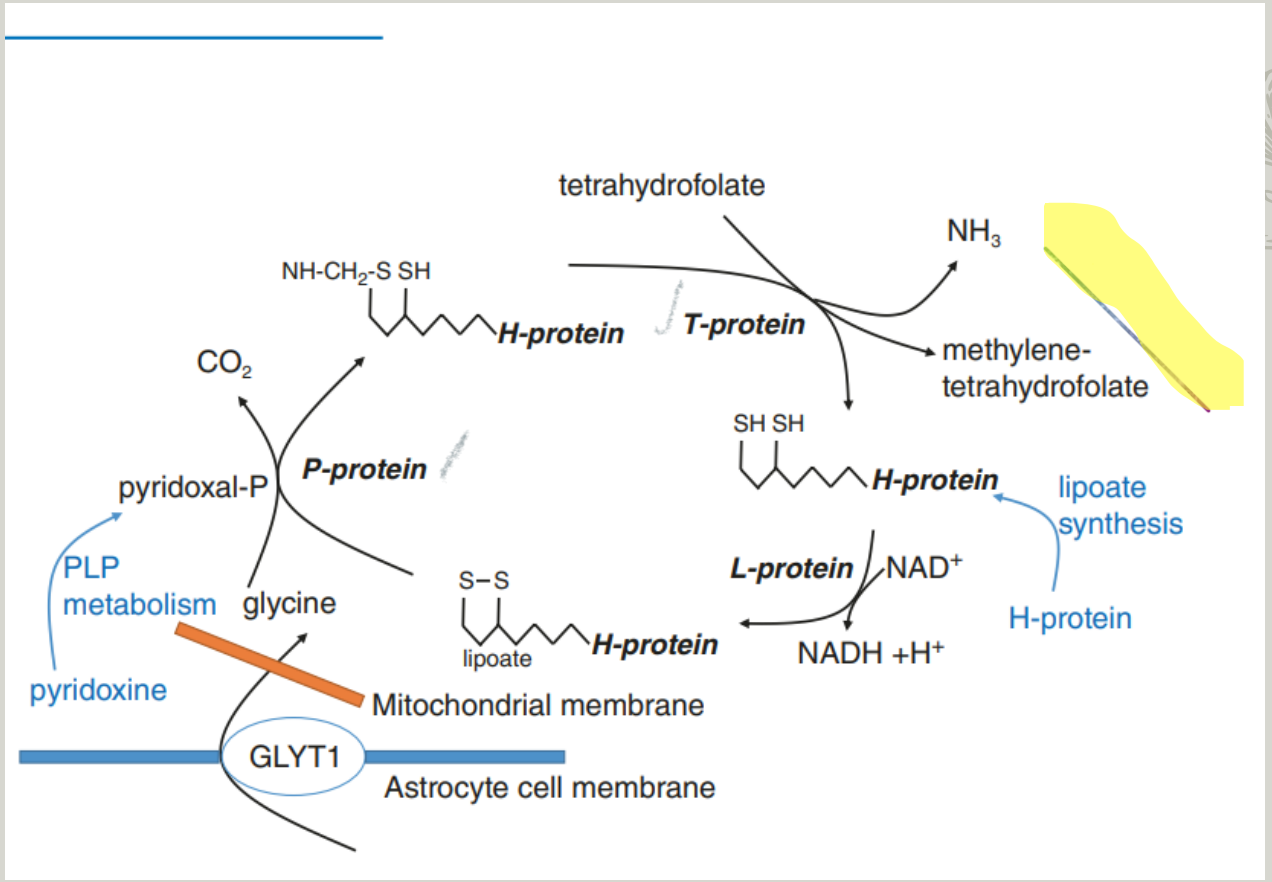




Glycine cleavage system . . *GLDC or AMT or Variant*

Variant NKH

- cofactor lipoic acid
- tetrahydrofolate
- Pyridoxin
- Glycine transport defect
- *cblX*



symptoms

- **Neonatal** (first hours to days of life) with progressive lethargy evolving into profound coma and marked hypotonia. In 80% of infants ventilatory drive slows, leading to prolonged apnea
- The vast majority of infants regain spontaneous respiration within the first three weeks of life, often with oral bottle drinking.
- Myoclonic jerks and hiccups are often a sign of epilepsy
- The initial EEG often shows a burst suppression pattern.

- **Infantile** (age >2 weeks to 3 months). While these infants do not have lethargy and coma in the first days of life, they often have a history of hypotonia from early on.
- They present with developmental delay and infantile-onset seizures that can be mild or increasingly difficult to treat.
- Infants with lethargy, hypotonia, seizures, poor feeding, developmental delays
  Children with developmental delays, hyperactivity , particularly with episodic worsening of manifestations

- **Late** (age >3 months) is rare, is always associated with the attenuated form, and involves developmental delays and possible mild seizures.

Atypical Form Symptoms.. Check glycine

- Seizures
- Abnormal muscle movements
- Intellectual disability
- Behavioral issues
- Attention-hyperactivity disorder
- Scoliosis
- Swallowing dysfunction
- Abnormal muscle tightness
- Gastroesophageal reflux

Classification

Severe NKH:

- Many infants never make any developmental gains
- limited interaction with their environment.
- progressive spasticity and cortical blindness
- Most have swallowing dysfunction
- Increasingly difficult-to-treat seizures
- Many develop scoliosis or hip dislocation
- Occasionally cleft palate or clubfeet .
- Some develop secondary microcephaly

Attenuated NKH :

- variable developmental progress.
- little spasticity.
- They may develop a seizure disorder, which is often relatively easy to treat
- Hyperactivity is common
- Many have choreic movements
- intermittent episodes of severe lethargy, often triggered by fever and infection (sometimes reported in the past as a "mild episodic form").

Eventually . .

- **Severe NKH.** Children make no developmental progress and have intractable epilepsy.
- **Attenuated NKH.** Children make variable developmental progress and have treatable or no epilepsy.

  Attenuated NKH is further divided into:

  - **Attenuated poor :** Children have a developmental quotient (DQ) of <20 and all have epilepsy.
  - **Attenuated intermediate :** Children have a DQ of 20 to 50 and easily treatable epilepsy or no epilepsy.
  - **Attenuated good :** Children have a DQ >50 and do not have epilepsy.

- **Neonatal onset.** 85% have severe NKH and 15% have attenuated NKH.
- **Infantile onset** (i.e., >2 weeks). 50% have severe NKH and 50% have attenuated NKH
- **Onset age >3 months.** All had attenuated NKH
- **The prevalence of nkh in the study of Dr. Salarian province was found to be 2.88 per 100,000 screenings in Fars.**

TRANSIENT

- Transient NKH is a phenocopy. In this clinical setting, neonates present with acute neurological symptoms and have elevated CSF glycine with often elevated CSF:plasma glycine levels. These elevated CSF glycine levels disappear spontaneously over the next days to weeks. There are no mutations present in the genes of the glycine cleavage enzyme and the GCS activity is normal. This feature can be seen in a variety of clinical settings, most commonly in hypoxic ischemic injury in a neonate
- The absence of the typical pattern of diffusion restriction of NKH indicates a phenocopy

Diagnosis

- Biochemical diagnosis is based on quantification of glycine levels in the plasma/serum and in the CSF, combined with urine organic acid analysis to rule out organic aciduria.
- CSF/plasma glycine levels are higher than 0.08 in the classic type of NKH and range from 0.04 to 0.02 in the atypical forms.
- Plasma glycine is often but not always elevated.

CSF glycine is always elevated with the elevation related to outcome, as a high CSF glycine is predictive of severe NKH

For this reason, lowering the blood level does not necessarily improve the neurological prognosis

Reference Values

Parameter	Control values <6 months	>6 months
Plasma glycine in µM	125–450	125–350
CSF glycine in µM	3–20	3–12
CSF-plasma glycine ratio	<0.02	<0.02

Pathological Values

Parameter	Severe NKH	Attenuated NKH	GLYT1
Plasma glycine in µM	1133 (342–2363)	822 (342–1590)	228; 275
CSF glycine in µM	228 (40–510)	99 (41–230)	25 (21–31)
CSF-plasma glycine ratio	0.22 (0.09–0.45)	0.13 (0.04–0.22)	0.07; 0.08

CSFglycine levels:

- Blood and brain glycine levels are high in newborns and decrease rapidly after 1 month
- Accurate measurement of CSF glycine requires that the CSF be completely free of contamination by blood or serum.
- The elevation of CSF glycine is more important than the ratio, which is only a secondary measure.
- In CSF, the serine concentration can be low, but the threonine concentration should not be elevated.
- The elevation of glycine levels in CSF in NKH is usually higher than that observed in disorders affecting the cofactors of the glycine cleavage enzyme system (lipoate, pyridoxal phosphate) and overlaps with attenuated NKH
- Documentation of a normal level of pyridoxal phosphate in the CSF helps to exclude disorders of pyridoxal phosphate metabolism

DDX

1. Hypoxic ischemic encephalopathy

2. Medications such as valproic acid and barbiturates which cause the elevation of glycine and burst suppression on EEG respectively.

3. Transient glycine encephalopathy

4. Organic acidemias may all cause elevations of glycine, however they are seen with a ketosis.

5. Elevations of glycine may be seen in the urine of patients with type I or type II hyperprolinemia, benign hyperglycinuria, or familial iminoglycinuria.

6. Pyridoximine 5′ phosphate oxidase deficiency giving rise to seizures produces a burst suppression on EEG

7. Other Inborn errors of metabolism giving rise to neonatal seizures such as peroxisome disorders, molybenum cofactor deficiency, Vitamin B6 and B9 dependent seizures, and phosphoglycerate dehydrogenase deficiency.

8. Liver failure

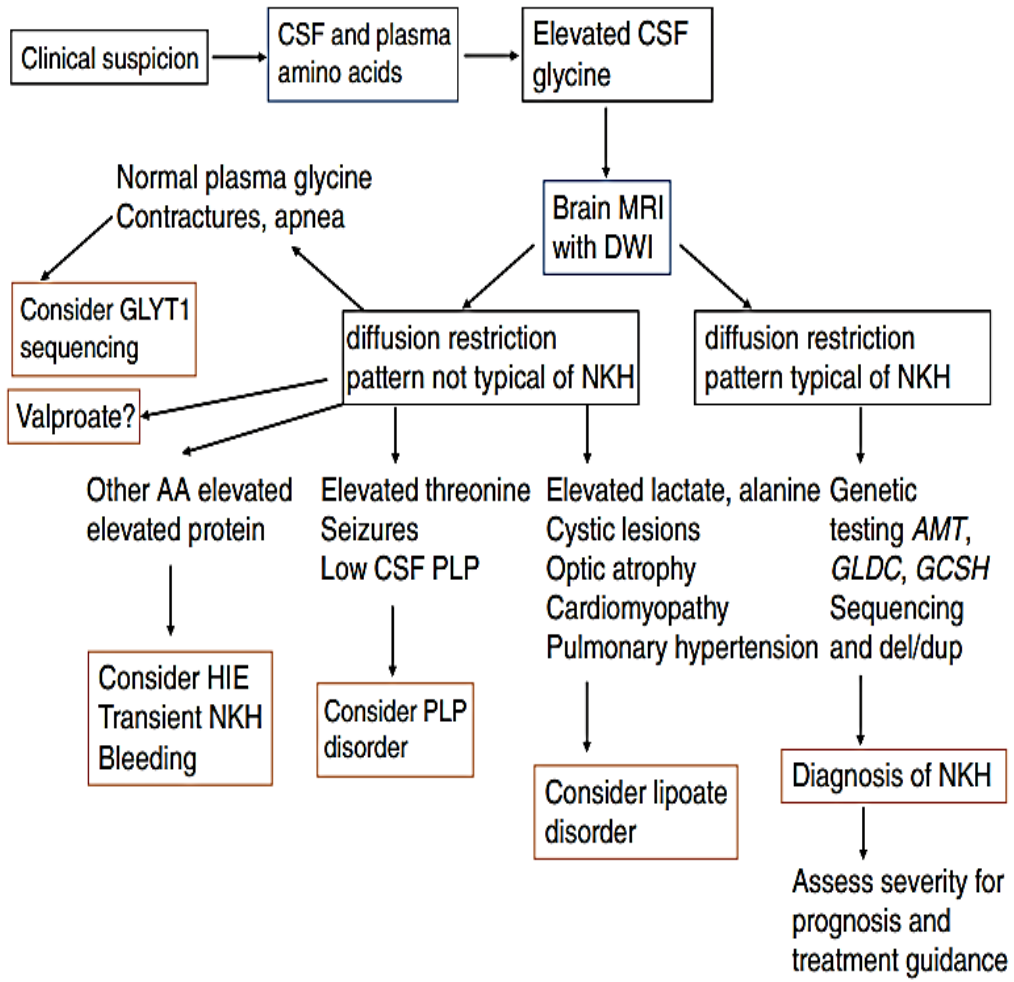
9. Immunoglobulins

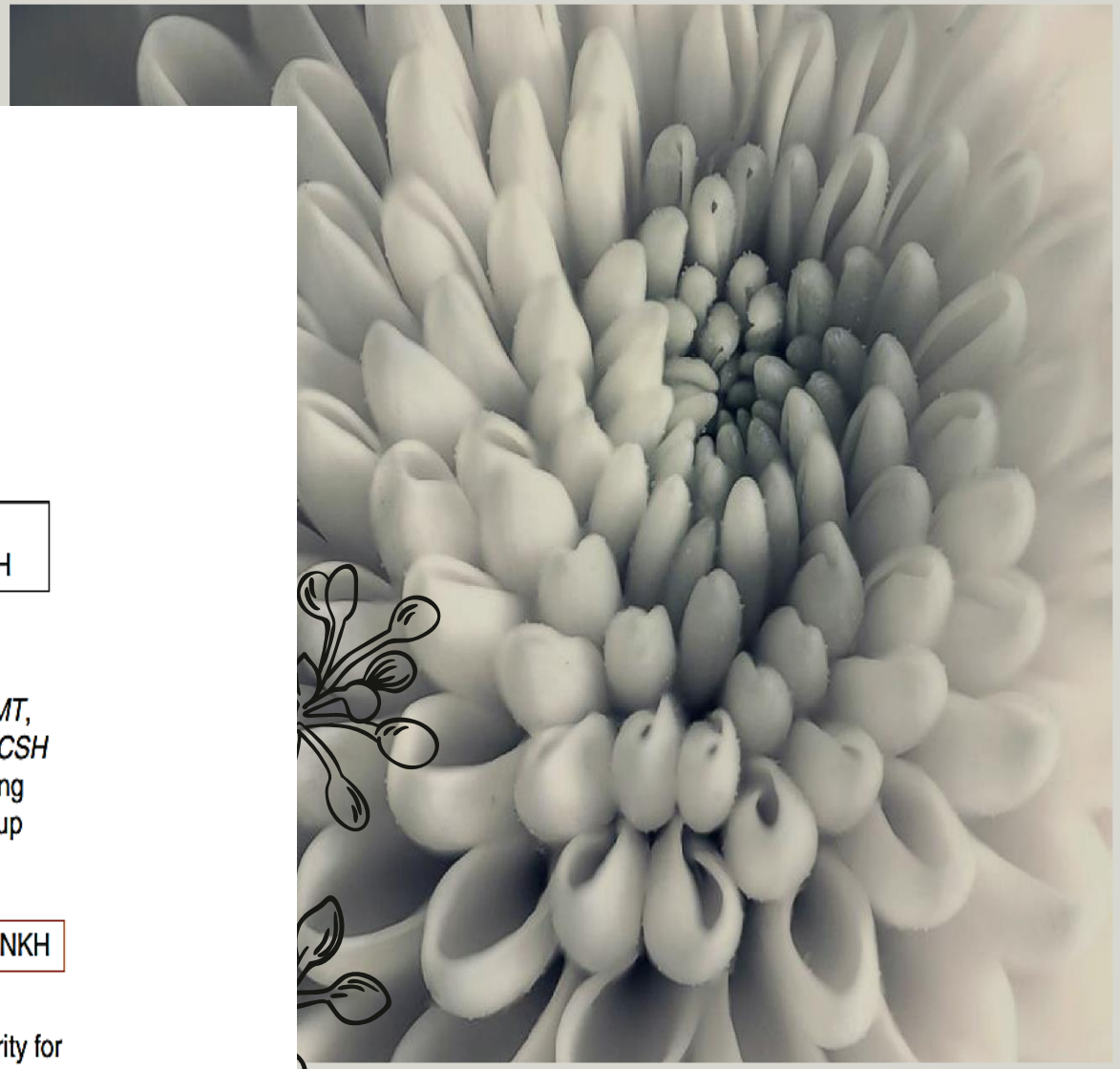
10. herpes virus infection

MRI (DWI)

- In the frst months of life
- diffusion restriction in the pyramidal tract in the posterior limb of the internal capsule and the anterior brain stem, in the posterior tegmental tract and cerebellum .
- This combination is highly suggestive of NKH and distinguishes the presentation from the transient NKH and from variant NKH
- show leukodystrophy or involvement of basal gangli It shows mitochondrial disorders
- Other:
  - The corpus callosum can be thin and shortened but is not absent.
  - A small group of infants develop hydrocephalus, often with an enlarged retrocerebellar cystic region.
  - Atrophy is present in older individuals with severe NKH, but often not in individuals with attenuated NKH.

Diagnostic Flowchart





Treatment

Current treatment is focused on:

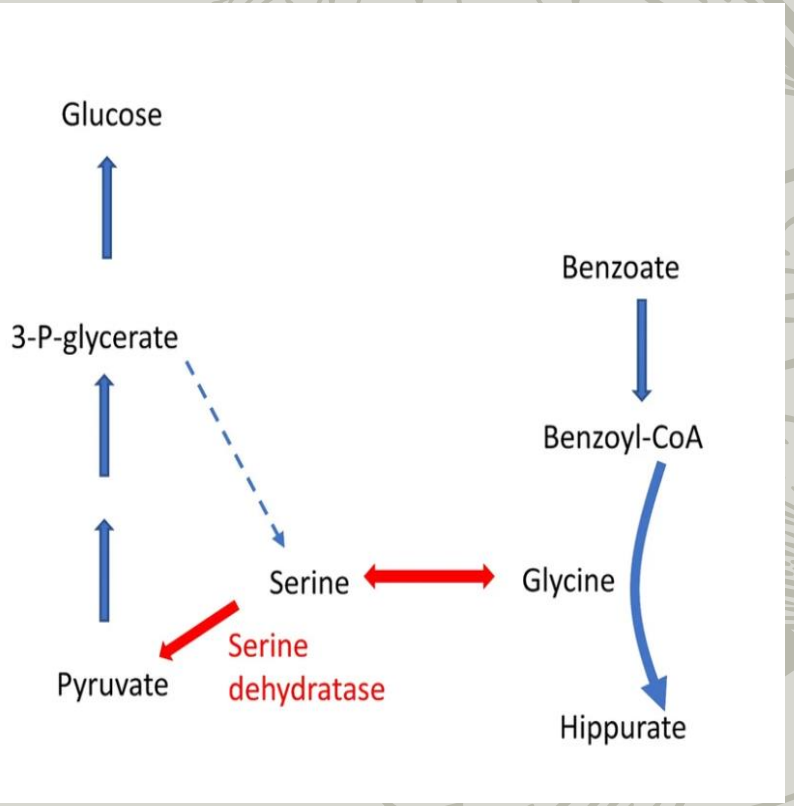
1) Reduction of plasma concentration of glycine
2) Use of N-methyl-D-aspartate (NMDA) receptor site antagonists
3) Symptomatic care

Other.

- Gastrostomy tube
- Gastroesophageal reflux is common. Some individuals have benefited from a Nissen procedure.
- Chronic obstipation, a frequent problem in severe NKH, can be treated with laxatives.
- Scoliosis and hip dislocation, common in older children with severe NKH, are managed with standard techniques.
- Individuals with severe NKH have progressive difficulty maintaining good airway management.
- Vigabatrin can cause rapid deterioration . ACTH treatment has not been effective in the treatment of West syndrome and is associated with worsening clinical status including inducing coma. Valproate is contraindicated in the patients with NKH.
-

Sodium benzoate

- can reduce the plasma glycine concentration into the normal range. The therapeutic goal is to lower the plasma glycine concentration into the low normal range, defined as 120 to 300 μmol/L for samples obtained one to two hours after a benzoate dose (timing is important).
- Individuals with attenuated NKH require a lower dose (200-550 mg/kg/day). For older children and adults, start at 5.5 g/m^2 BSA.
- Individuals with severe NKH require a higher dose (550-750 mg/kg/day) for adults, maximum 16.5 g/m^2/day.
- Sodium benzoate should be divided into no less than three doses per day; doses are more frequent in infancy (for example, neonates typically receive six daily doses).



- If the plasma glycine concentration is not within target range, the dose is increased by 50 mg/kg/day, and plasma glycine concentration is measured again as soon as 48 hours later. When glycine is within the target range, plasma glycine levels are measured regularly:
  - every two weeks for infants,
  - every month for young children
  - every three months for older children.
- Because the liver and kidney (but not the brain) are the sites of action of sodium benzoate,It is known that treatment with sodium benzoate does not normalize CSF glycine concentration. Follow up with serial measurements of CSF glycine concentration is not required.
- High-dose sodium benzoate (500-750 mg/kg/day) is frequently associated with gastritis, which may require oral administration of antacids, H_2 antagonists, or proton pump inhibitors.
- High-dose sodium benzoate in young infants can be associated with excessive loss of carnitine; those with low carnitine levels should receive supplementation to maintain normal plasma concentrations.
- Dosing of sodium benzoate in excess of the individual requirement is dangerous: benzoate toxicity has high morbidity and mortality .Hypocalcemia and low plasma glycine concentration (<150 μmol/L) can be early signs of sodium benzoate overdose.
- As benzoate is unpalatable, a saliva-resistant granulated benzoate is available in several countries

NMDA Receptor Site Antagonists

Dextromethorphan

- doses commonly range from 3 to 15 mg/kg/day, but individual variability is substantial. typically started at 10 mg/kg/day for neonates, 5 mg/kg/day for children, and 3 mg/kg/day for adolescents and adults, administered in three or four doses per day
- cimetidine not used as they may cause toxicity
- dextromethorphan can cause increases in sleepiness and movement.

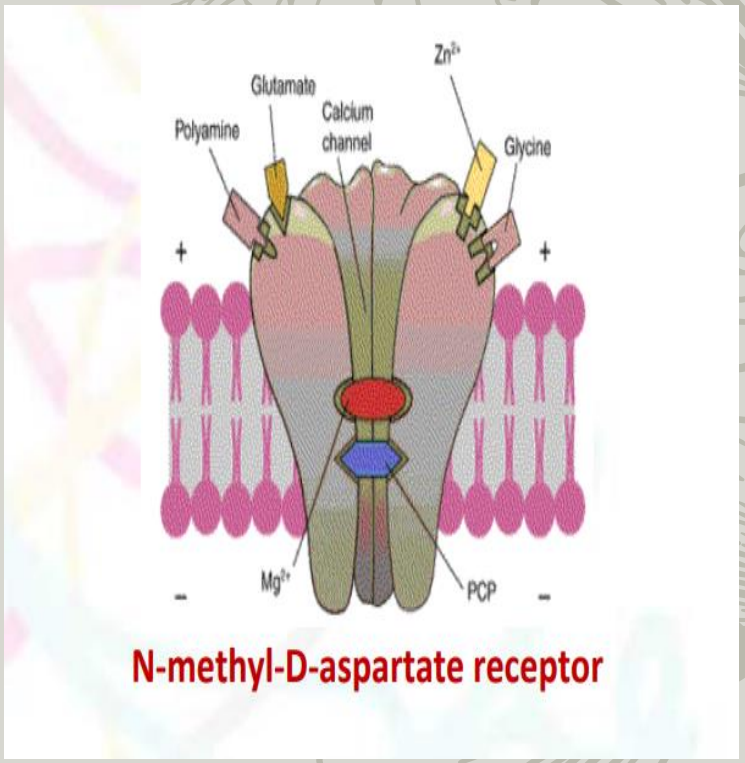
❖ **Attenuated NKH**. Dextromethorphan used in combination with sodium benzoate has improved neurocognitive outcome and decreased seizure propensity. Improved attention, school performance, and behavior, as well as decreased chorea, have been observed in several individuals with attenuated NKH . In itself, high-dose dextromethorphan may have some anticonvulsant activity.

❖ **Severe NKH.** In patients with severe NKH, dextromethorphan is less effective or ineffective and may result in recurrent pneumonia, presumably due to decreased coughing

- An alternative lipophilic non-competitive NMDA receptor blocker is ketamine

Oral ketamine

- , used in oral application at daily doses of 15 mg/kg in neonates, reduced to 9 mg/kg/day in infants (range: 1–32 mg/kg) with improved cognitive outcome in case of early treatment in attenuated mutation carriers.



Diet . .

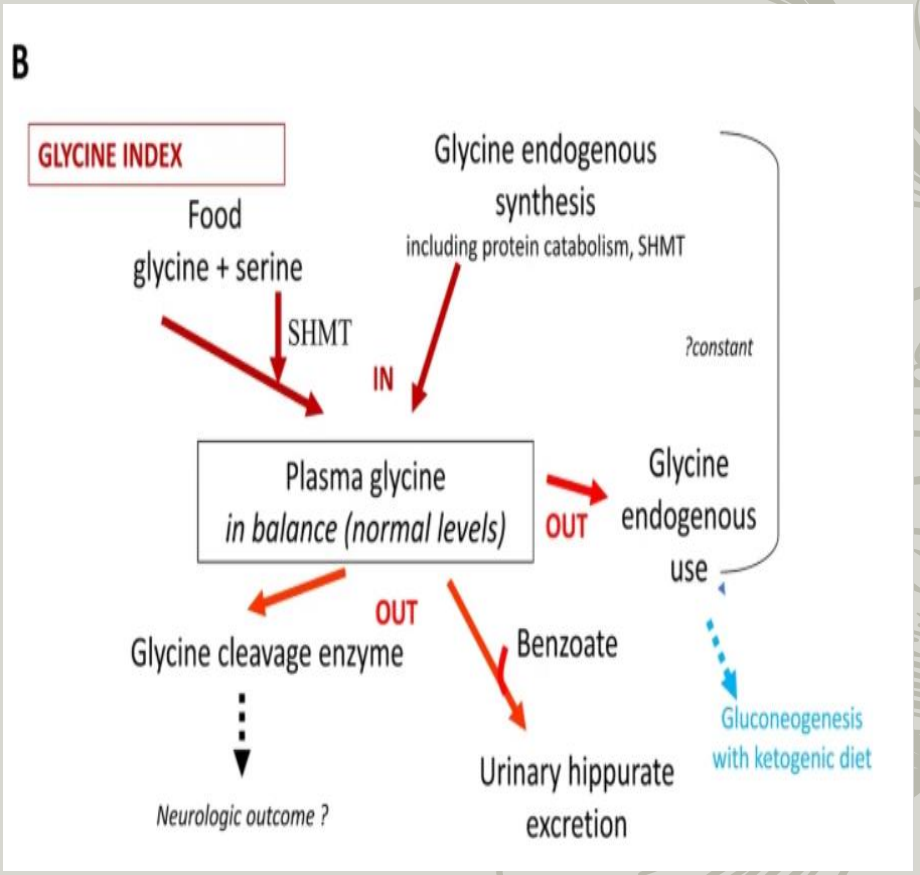
❖ **Glycine-restricted diet.** contribution of dietary glycine is small compared to the excess in endogenous glycine synthesis versus endogenous catabolism of glycine.

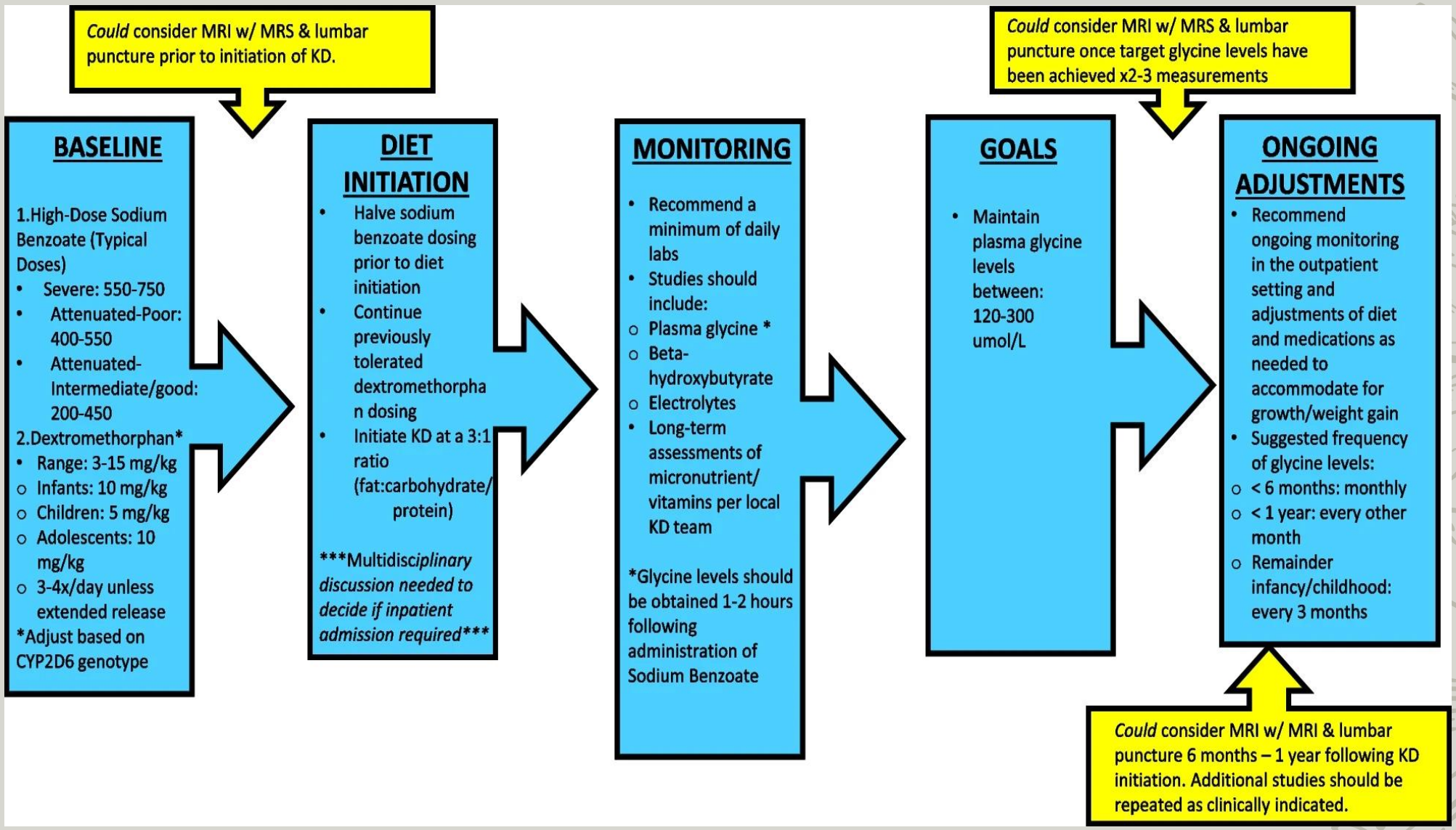
- Infant formula is typically low in glycine; advancing the diet to intake of solid food introduces a small amount of extra dietary glycine.
- Restriction of dietary glycine can aid in controlling plasma glycine levels for some individuals with severe NKH. For many individuals a mild increase in the dose of sodium benzoate compensates for increased dietary intake of glycine.
- An inappropriately severe glycine-restricted diet has been associated with protein malnutrition
- The clinical effect of this form of glycine restriction is only partially described, and includes a decrease of seizures, increased alertness with variable effect on the EEG pattern..

❖ **Ketogenic diet**

Ketogenic diet always lowers the amount of glycine substantially and the dose of sodium benzoate should be reduced accordingly to avoid benzoate toxicity . Ketogenic diet has resulted in improved seizure control, but did not change hypsarrhythmic background.

- * Note: Because the glycine pool is reduced when individuals are on a ketogenic diet, sodium benzoate dose must be reduced upon initiation of this diet to avoid toxicity.




Could consider MRI w/ MRS & lumbar puncture prior to initiation of KD.
BASELINE
1.High-Dose Sodium Benzoate (Typical Doses)
• Severe: 550-750
• Attenuated-Poor: 400-550
• Attenuated-Intermediate/good: 200-450
2.Dextromethorphan*
• Range: 3-15 mg/kg
o Infants: 10 mg/kg
o Children: 5 mg/kg
o Adolescents: 10 mg/kg
o 3-4x/day unless extended release
*Adjust based on CYP2D6 genotype
DIET INITIATION
• Halve sodium benzoate dosing prior to diet initiation
• Continue previously tolerated dextromethorphan dosing
• Initiate KD at a 3:1 ratio (fat:carbohydrate/protein)
Multidisciplinary discussion needed to decide if inpatient admission required
MONITORING
• Recommend a minimum of daily labs
• Studies should include:
o Plasma glycine *
o Beta-hydroxybutyrate
o Electrolytes
• Long-term assessments of micronutrient/vitamins per local KD team
*Glycine levels should be obtained 1-2 hours following administration of Sodium Benzoate
GOALS
• Maintain plasma glycine levels between: 120-300 umol/L
Could consider MRI w/ MRS & lumbar puncture once target glycine levels have been achieved x2-3 measurements
ONGOING ADJUSTMENTS
• Recommend ongoing monitoring in the outpatient setting and adjustments of diet and medications as needed to accommodate for growth/weight gain
• Suggested frequency of glycine levels:
o < 6 months: monthly
o < 1 year: every other month
o Remainder infancy/childhood: every 3 months
Could consider MRI w/ MRI & lumbar puncture 6 months – 1 year following KD initiation. Additional studies should be repeated as clinically indicated.

- For severe NKH, no treatment is effective in changing the natural history of developmental delays, spasticity, and intractable epilepsy. Specifically, glycine-lowering therapy is not effective in improving the affected individual's development, even when initiated at birth

  However, glycine-lowering therapy does decrease the frequency and severity of seizures and is used as part of the overall epilepsy management of disease . It also improves attentiveness and resolves neonatal apnea.

- In contrast, for attenuated NKH aggressive treatment of children with pathogenic variants associated with residual glycine cleavage enzyme system (GCS) activity who are likely to develop attenuated NKH resulted in improved neurodevelopmental outcome and reduced propensity for epilepsy .

GLDC ..exon21
c.2458A>G
p.M820V

هو الشافی

شماره : .....
تاریخ : ۱۴۰۱/۰۶/۳۰
پیوست : .....

مرکز جامع ژنتیک پزشکی جنوب کشور (شهید سلطانی)
Comprehensive Medical Genetics Center
BS EN ISO 9001:2015

Proband: دریا نجاتی (اصغر)

Molecular Lab No: 7322

Requested Assay: Target following mutation analysis:

Gene	Transcript	Variation
GLDC	NM_000170.3	c.2458A>G, p.M820V
CCDC47	NM_020198.3	c.1188C>G, p.F396L

Sample: Genomic DNA isolated from EDTA blood
Requested by: دکتر مریم تقدیری
Date Sample Received: 12.4.1401
Methods: Sequencing

Results:

Gene	Chromosome	Variation	Genotype	Mode of Inheritance
GLDC	9	c.2458A>G, p.M820V	**Homozygous mutation**	AR
CCDC47	17	c.1188C>G, p.F396L	**Homozygous mutation**	AR

Variation analysis:

Gene	Variation	Sift	Mutation taster	Polyphen	Provean	ACMG	Associated disease
GLDC	c.2458A>G, p.M820V	Damaging	Deleterious	Probably damaging	Damaging	Pathogenic/ VUS	Glycine encephalopathy
CCDC47	c.1188C>G, p.F396L	Tolerated	Benign	Benign	Damaging	VUS	Trichohepatoneurodevelopmental syndrome

Recommendation: Proband and his family need a proper consultation.
Limitations: Large deletions, duplications, mutations in regulatory regions and not requested regions were not investigated.

Additional Comments: It is of utmost importance for all clinicians involved in the care of families requesting molecular genetics diagnostic tests and the families themselves to be aware of the risk of errors in DNA analysis. Incorrect analysis may result from 1) incorrect data and clinical diagnosis 2) incomplete family studies and history 3) mix-up of DNA samples and mislabeling 4) rare molecular events5) new or spontaneous mutations 6) paternity problems, adaptation, IVF, egg donor, bone marrow transplantation, recent blood product transfusion 7) maternal DNA contamination of CVS or amniotic fluid samples 8) technical errors. The risk of errors from various reasons mentioned above and several others is about 0.5%, while the chance of technical errors of all types is estimated to be around 0.5%. The risk of errors due to DNA recombination in diagnosis is approximately 0.3%. We take no responsibility about patient identity and possible mislabeling of the DNA samples. Any feedback from our colleagues in the clinical field would be most welcomed. Comments can be given in writing or by e-mail to: m.entezam@gmail.com
It should be noted that the classification of the above mentioned variant is based on current findings and there is a possibility to change in the future. Co-segregation of the above mentioned variant is highly recommended for the other affected members of the family and this evidence may help to reclassification of reported variant.

Dr. Mona Entezam
Medical Geneticist
Comprehensive Medical Genetics Center,
Shiraz University of Medical Sciences,
Shiraz, Iran

مرکز جامع ژنتیک پزشکی جنوب کشور
دکتر مونا انتظام
متخصص ژنتیک پزشکی - استاد یار تمام وقت
شماره پزشک ۳۸۴۲

شیراز : خیابان قصردشت / جنب پایگاه منطقه ای اورژانس فارس/ نبش کوچه ۹۳ / مرکز جامع ژنتیک پزشکی جنوب کشور (شهید سلطانی)
تلفن : ۲۲ -۳۶۳۰۳۴۲۱- ۰۷۱
www.shirazgen.ir info@shirazgen.ir

تشکر از صبر
وحوصله سروران
جان