
به نام خدا

A treatable neurodevelopmental disease

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CASE REPORT

- علت ارجاع:رشد ناکافی دور سر
- شیرخوار دختر ۲ ماهه با وزن تولد: ۲۷۰۰ گرم،قد :۴۸ سانتیمتر و دورسر ۳۳ سانتیمتر
- حاصل سزارین
- G2L2
- والدین منسوب

CASE REPORT

- در سیر تکاملی بیمار در ۴ ماهگی گردن میگیرد و با تاخیر می نشیند.
- در سن ۱۰ ماهگی:

❖ وزن: ۷۷۵۰ گرم (Z-SCORE: -1)

❖ قد: ۶۸ سانتیمتر (Z-SCORE: -1)

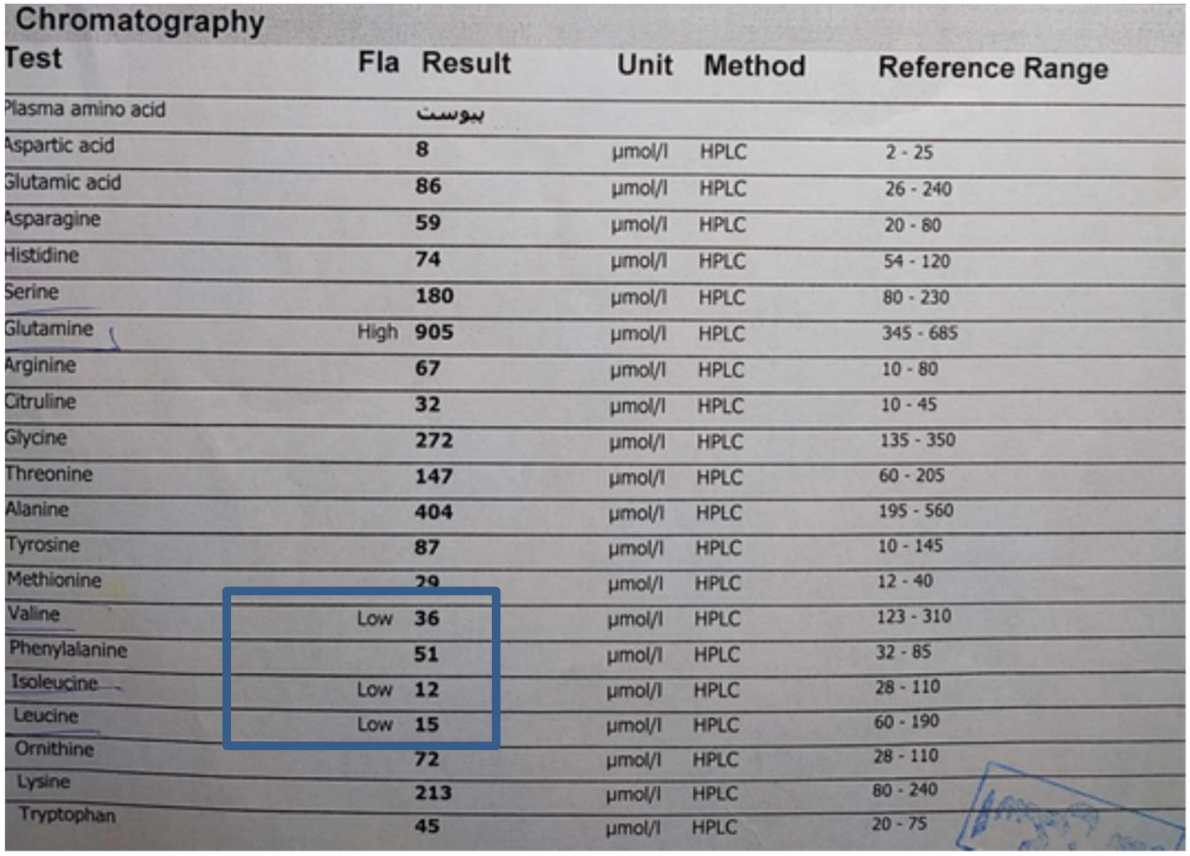
❖ دور سر: ۴۱ سانتیمتر (Z-SCORE: -3)

❖ سونوگرافی شکم و مغز : نرمال

❖ آزمایشات اولیه رشد : نرمال

که با توجه به شرایط بیمار **آزمایشات تکمیلی متابولیک** فرستاده شد

Case report



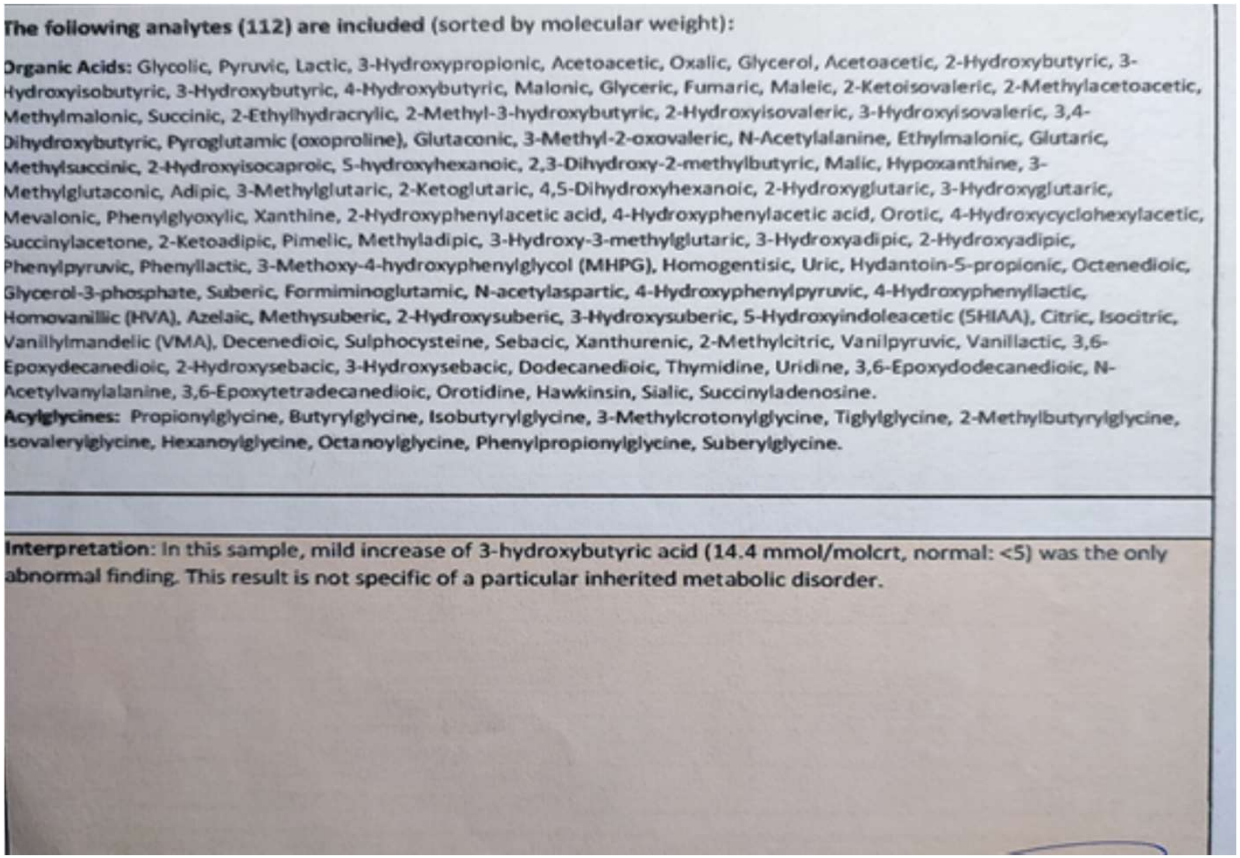
Chromatography

Test	Fla	Result	Unit	Method	Reference Range
Plasma amino acid		پیوست			
Aspartic acid		8	µmol/l	HPLC	2 - 25
Glutamic acid		86	µmol/l	HPLC	26 - 240
Asparagine		59	µmol/l	HPLC	20 - 80
Histidine		74	µmol/l	HPLC	54 - 120
Serine		180	µmol/l	HPLC	80 - 230
Glutamine	High	905	µmol/l	HPLC	345 - 685
Arginine		67	µmol/l	HPLC	10 - 80
Citruline		32	µmol/l	HPLC	10 - 45
Glycine		272	µmol/l	HPLC	135 - 350
Threonine		147	µmol/l	HPLC	60 - 205
Alanine		404	µmol/l	HPLC	195 - 560
Tyrosine		87	µmol/l	HPLC	10 - 145
Methionine		29	µmol/l	HPLC	12 - 40
Valine	Low	36	µmol/l	HPLC	123 - 310
Phenylalanine		51	µmol/l	HPLC	32 - 85
Isoleucine	Low	12	µmol/l	HPLC	28 - 110
Leucine	Low	15	µmol/l	HPLC	60 - 190
Ornithine		72	µmol/l	HPLC	28 - 110
Lysine		213	µmol/l	HPLC	80 - 240
Tryptophan		45	µmol/l	HPLC	20 - 75

Plasma aminoacid

Amino Acid	Result (µM)	Normal Value	Description
Alanine	380.4	139-474	Normal
Allo-isoleucine	0.3	<2	Normal
Alpha-aminoadipic acid	2.1	<4	Normal
Arginine	60.2	29-114	Normal
Argininosuccinic acid	0.0	<0.2	Normal
Asparagine	52.6	25-91	Normal
Aspartic acid	12.5	<20	Normal
Beta-aminoisobutyric acid	3.1	<5	Normal
Beta-alanine	19.3	<28	Normal
Citrulline	11.2	9-38	Normal
Cystathionine	0.3	<0.5	Normal
Cystine	18.3	2-25	Normal
Gamma-aminobutyric acid	0.5	<1.5	Normal
Glutamic acid	86.4	31-202	Normal
Glutamine	732.1	316-880	Normal
Glycine	268.2	111-426	Normal
Glycylproline	0.1	<1	Normal
Histidine	74.8	10-116	Normal
Homocitrulline	0.5	<2	Normal
Homocystine	0.1	<0.5	Normal
Hydroxylysine	0.1	<1	Normal
Hydroxyproline	41.9	8-61	Normal
Isoleucine	*11.0*	*22-105*	*Abnormal*
Leucine	*18.6*	*48-175*	*Abnormal*
Lysine	192.5	49-204	Normal
Methionine	25.9	11-45	Normal
Ornithine	67.3	20-130	Normal
Phenylalanine	51.8	28-98	Normal
Proline	253.7	85-303	Normal
Serine	242.1	69-271	Normal
Sulfocysteine	0.0	<0.4	Normal
Threonine	114.5	47-237	Normal
Tryptophan	60.2	17-75	Normal
Tyrosine	54.8	26-115	Normal
Valine	*42.9*	*83-312*	*Abnormal*

Urine organic acid



The following analytes (112) are included (sorted by molecular weight):

Organic Acids: Glycolic, Pyruvic, Lactic, 3-Hydroxypropionic, Acetoacetic, Oxalic, Glycerol, Acetoacetic, 2-Hydroxybutyric, 3-Hydroxyisobutyric, 3-Hydroxybutyric, 4-Hydroxybutyric, Malonic, Glyceric, Fumaric, Maleic, 2-Ketoisovaleric, 2-Methylacetoacetic, Methylmalonic, Succinic, 2-Ethylhydracrylic, 2-Methyl-3-hydroxybutyric, 2-Hydroxyisovaleric, 3-Hydroxyisovaleric, 3,4-Dihydroxybutyric, Pyroglutamic (oxoproline), Glutaconic, 3-Methyl-2-oxovaleric, N-Acetylalanine, Ethylmalonic, Glutaric, Methylsuccinic, 2-Hydroxyisocaproic, 5-hydroxyhexanoic, 2,3-Dihydroxy-2-methylbutyric, Malic, Hypoxanthine, 3-Methylglutaconic, Adipic, 3-Methylglutaric, 2-Ketoglutaric, 4,5-Dihydroxyhexanoic, 2-Hydroxyglutaric, 3-Hydroxyglutaric, Mevalonic, Phenylglyoxylic, Xanthine, 2-Hydroxyphenylacetic acid, 4-Hydroxyphenylacetic acid, Orotic, 4-Hydroxycyclohexylacetic, Succinylacetone, 2-Ketoadipic, Pimelic, Methyladipic, 3-Hydroxy-3-methylglutaric, 3-Hydroxyadipic, 2-Hydroxyadipic, Phenylpyruvic, Phenyllactic, 3-Methoxy-4-hydroxyphenylglycol (MHPG), Homogentisic, Uric, Hydantoin-5-propionic, Octenedioic, Glycerol-3-phosphate, Suberic, Formiminoglutamic, N-acetylaspartic, 4-Hydroxyphenylpyruvic, 4-Hydroxyphenyllactic, Homovanillic (HVA), Azelaic, Methysuberic, 2-Hydroxysuberic, 3-Hydroxysuberic, 5-Hydroxyindoleacetic (5HIAA), Citric, Isocitric, Vanillylmandelic (VMA), Decenedioic, Sulphocysteine, Sebacic, Xanthurenic, 2-Methylcitric, Vanilpyruvic, Vanillactic, 3,6-Epoxydecanedioic, 2-Hydroxysebacic, 3-Hydroxysebacic, Dodecanedioic, Thymidine, Uridine, 3,6-Epoxydodecanedioic, N-Acetylvanylalanine, 3,6-Epoxytetradecanedioic, Orotidine, Hawkinsin, Sialic, Succinyladenosine.

Acylglycines: Propionylglycine, Butyrylglycine, Isobutyrylglycine, 3-Methylcrotonylglycine, Tiglylglycine, 2-Methylbutyrylglycine, Isovalerylglycine, Hexanoylglycine, Octanoylglycine, Phenylpropionylglycine, Suberylglycine.

Interpretation: In this sample, mild increase of 3-hydroxybutyric acid (14.4 mmol/molcrt, normal: <5) was the only abnormal finding. This result is not specific of a particular inherited metabolic disorder.

Plasma acylcarnitine

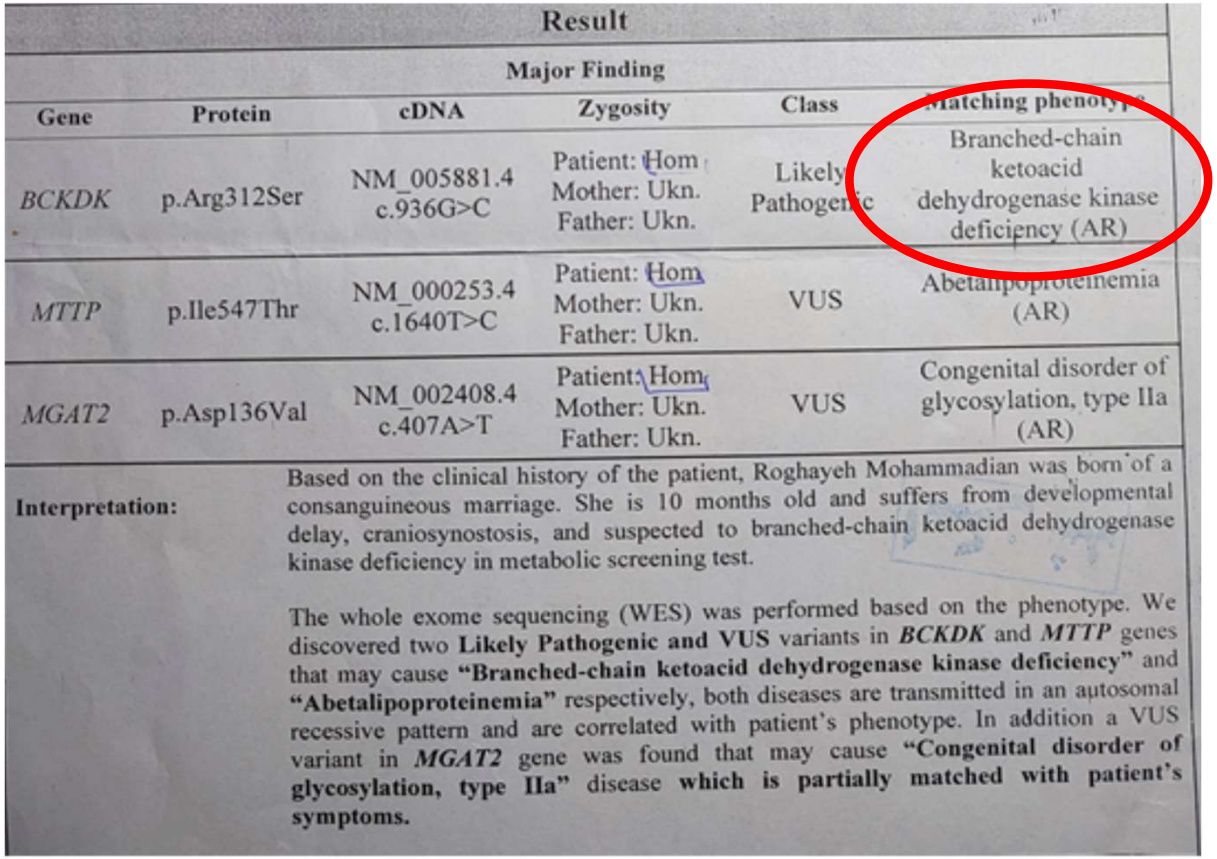
Analyte	Analyte Full name	Result (μM)	Normal Value	Description
C0	Free Carnitine	13.08	7.6-32	Normal
C2	Acetylcarnitine	6.73	1.5-12	Normal
C3	Propionylcarnitine	0.25	<0.62	Normal
C3DC+C8OH	(Malonyl+hydroxyoctanoyl)carnitine	0.05	<0.28	Normal
C4	(Butyryl+Isobutyryl)carnitine	0.12	<0.32	Normal
C4OH	Hydroxy(butyryl+isobutyryl)carnitine	0.07	<0.16	Normal
C4DC	(Succinyl+methylmalonyl)carnitine	0.03	<0.20	Normal
C5	(Isovaleryl+methylbutyryl)carnitine	0.03	<0.26	Normal
C5:1	Tiglylcarnitine	0	<0.03	Normal
C5OH	Hydroxy(isovaleryl+methylbutyryl)carnitine	0.01	<0.07	Normal
C5DC+C10OH	(Glutaryl+Hydroxydecanoyl)carnitine	0.05	<0.15	Normal
C6	Hexanoylcarnitine	0.03	<0.10	Normal
C6OH	Hydroxyhexanoylcarnitine	0.01	<0.08	Normal
C6DC	(Methylglutaryl+Adipoyl)carnitine	0.05	<0.15	Normal
C8	Octanoylcarnitine	0.05	<0.18	Normal
C8:1	Octenoylcarnitine	0.06	<0.34	Normal
C10	Decanoylcarnitine	0.06	<0.26	Normal
C10:1	Decenoylcarnitine	0.07	<0.36	Normal
C10:2	Decadienoylcarnitine	0.01	<0.10	Normal
C12	Dodecanoylcarnitine	0.02	<0.18	Normal
C12:1	Dodecenoylcarnitine	0.01	<0.25	Normal
C14	Tetradecanoylcarnitine	0.02	<0.15	Normal
C14:1	Tetradecenoylcarnitine	0.02	<0.20	Normal
C14:2	Tetradecadienoylcarnitine	0.01	<0.08	Normal
C14OH	Hydroxytetradecanoylcarnitine	0.01	<0.03	Normal
C16	Hexadecanoylcarnitine	0.05	0.01-0.12	Normal
C16:1	Hexadecenoylcarnitine	0.01	<0.07	Normal
C16OH	Hydroxyhexadecanoylcarnitine	0	<0.03	Normal
C16:1OH	Hydroxyhexadecenoylcarnitine	0	<0.05	Normal
C18	Octadecanoylcarnitine	0.02	<0.10	Normal
C18:1	Octadecenoylcarnitine	0.03	0.01-0.14	Normal
C18:2	Octadecadienoylcarnitine	0.01	<0.08	Normal
C18OH	Hydroxyoctadecanoylcarnitine	0	<0.02	Normal
C18:1OH	Hydroxyoctadecenoylcarnitine	0	<0.02	Normal

Interpretation: No abnormality.

TREATMENT

- **مشاوره تغذیه** درخواست شد و درمان جایگزینی اسید آمینه های ضروری برای بیمار شروع شد و توصیه به انجام بررسی **ژنتیک** شد.

WES



Result

Major Finding

Gene	Protein	cDNA	Zygosity	Class	Matching phenotype
BCKDK	p.Arg312Ser	NM_005881.4 c.936G>C	Patient: Hom Mother: Ukn. Father: Ukn.	Likely Pathogenic	Branched-chain ketoacid dehydrogenase kinase deficiency (AR)
MTTP	p.Ile547Thr	NM_000253.4 c.1640T>C	Patient: Hom Mother: Ukn. Father: Ukn.	VUS	Abetalipoproteinemia (AR)
MGAT2	p.Asp136Val	NM_002408.4 c.407A>T	Patient: Hom Mother: Ukn. Father: Ukn.	VUS	Congenital disorder of glycosylation, type IIa (AR)

Interpretation:

Based on the clinical history of the patient, Roghayeh Mohammadian was born of a consanguineous marriage. She is 10 months old and suffers from developmental delay, craniosynostosis, and suspected to branched-chain ketoacid dehydrogenase kinase deficiency in metabolic screening test.

The whole exome sequencing (WES) was performed based on the phenotype. We discovered two **Likely Pathogenic and VUS** variants in ***BCKDK*** and ***MTTP*** genes that may cause **"Branched-chain ketoacid dehydrogenase kinase deficiency"** and **"Abetalipoproteinemia"** respectively, both diseases are transmitted in an autosomal recessive pattern and are correlated with patient's phenotype. In addition a VUS variant in ***MGAT2*** gene was found that may cause **"Congenital disorder of glycosylation, type IIa"** disease **which is partially matched with patient's symptoms.**

TREATMENT

- **BCAA**
- **Isoleucin**
- **Valine**

سن ۱۸ ماهگی:

- **وزن:** ۸۸۰۰ گرم (Z-SCORE: -1)
- **قد:** ۷۶ سانتیمتر (Z-SCORE: -1تا-2)
- **دور سر:** ۴۲ سانتیمتر (Z-SCORE: -3)

چهار دست و پا راه میرود، هنوز نمی ایستد و میکروسفالی دارد.

مشاوره نورولوژی : EEG نرمال

Follow up

Leucine	21	110
Isoleucine	10	66
Valine	44	217

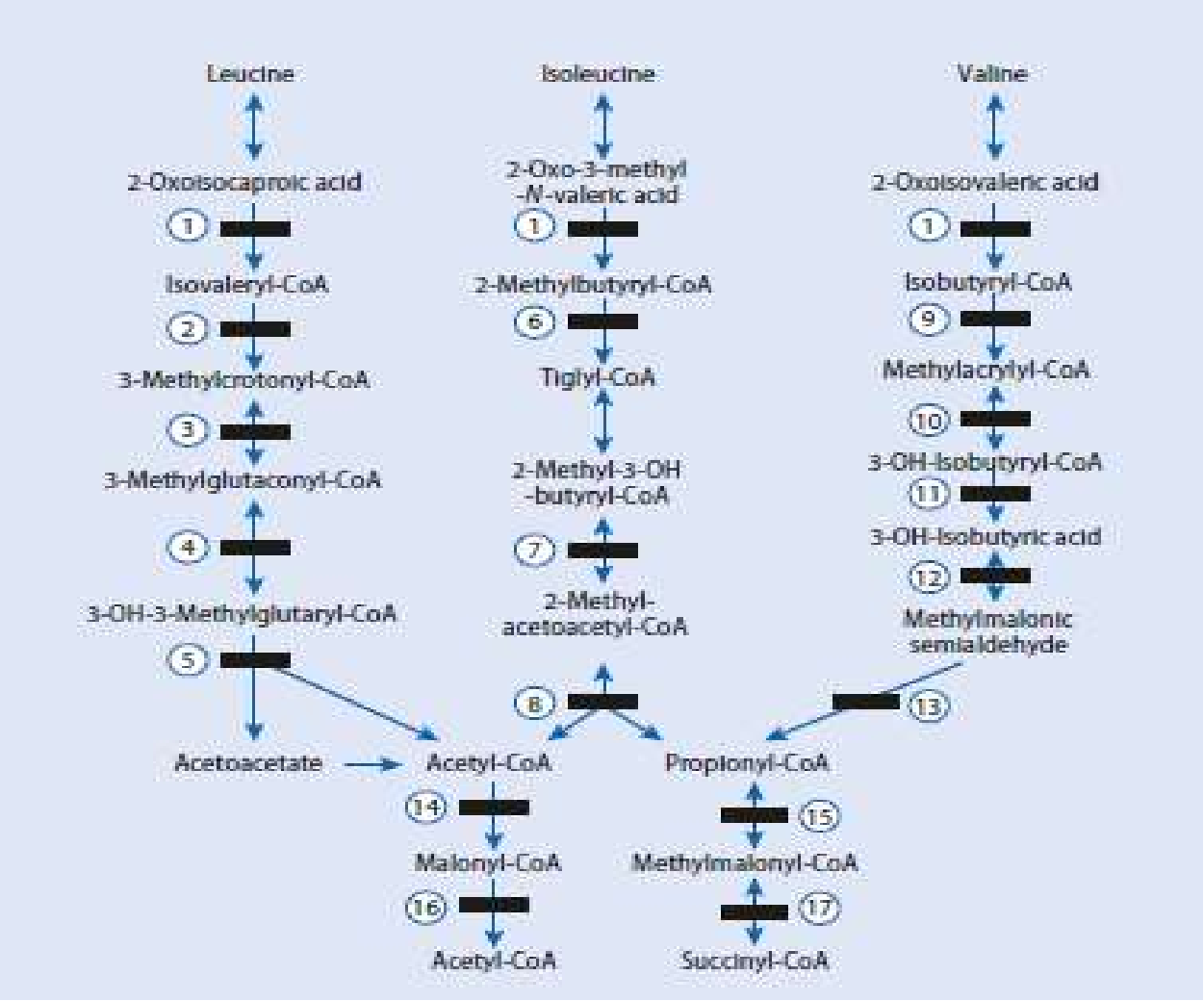
BCAA

- Branched-chain amino acids are essential amino acids involved in :
- vital cellular reactions such as protein turnover regulation, autophagy signalling, mitochondrial function and neurotransmitter metabolism

BCAA metabolism

- The first reaction, which occurs primarily in muscle:
- reversible transamination to 2-oxo- (or keto) acids
- followed by oxidative decarboxylation to CoA derivatives by BCKD

BCAA pathway



BCAA metabolism

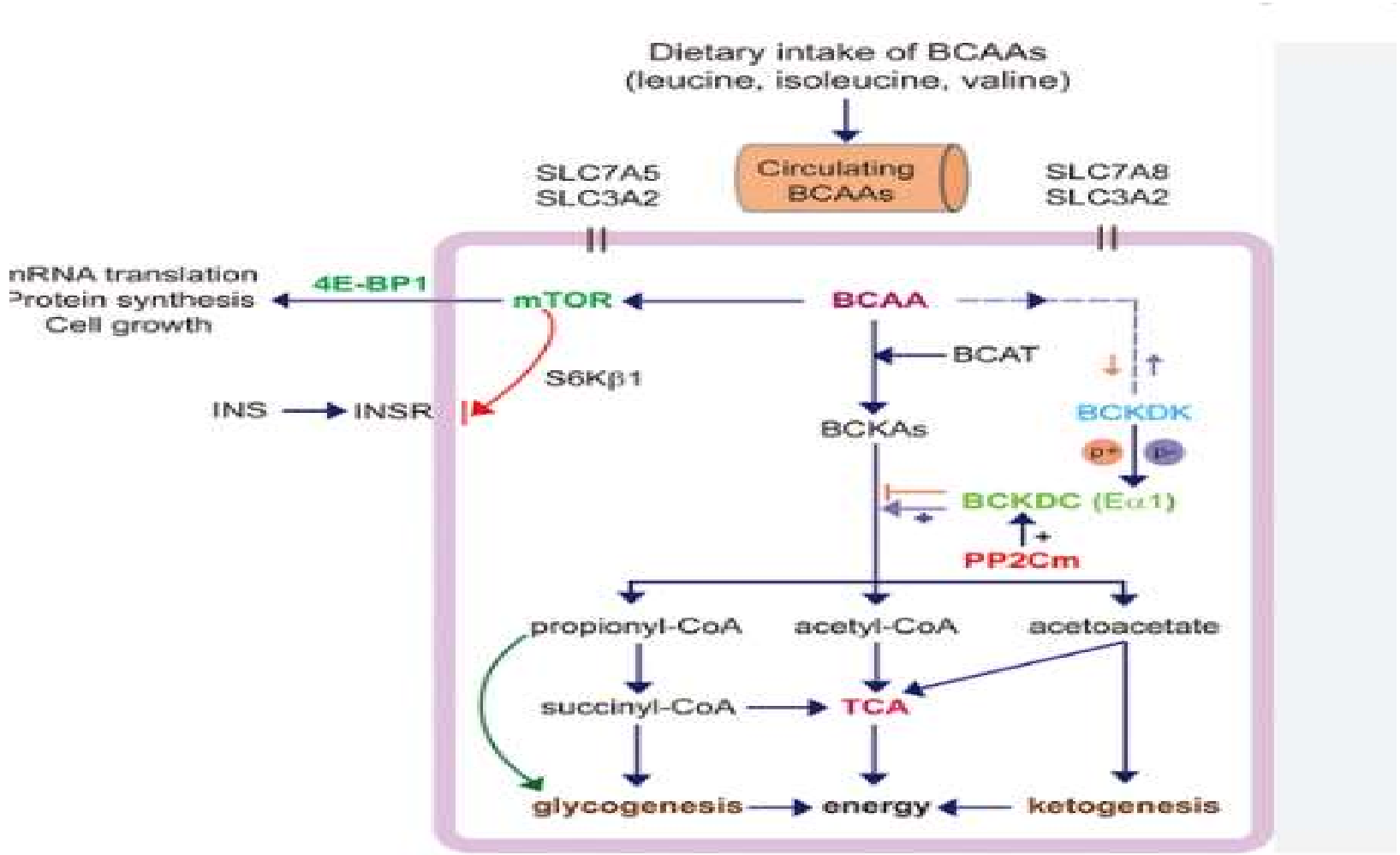
- Leucine →acetoacetate and acetyl-CoA: Krebs cycle
- Isoleucine :acetyl-CoA and propionyl-CoA : Krebs cycle via conversion into succinyl-CoA
- Valine →propionyl-CoA

BCAA metabolism

- The branched-chain ketoacid dehydrogenase (BCKDH) complex catalyzes the irreversible, rate-limiting step in the catabolism of BCAAs

- BCKDK encodes a kinase that phosphorylates and thus inactivates the E1α subunit of this complex

BCAA pathway



BCKD KINASE DEFICIENCY

- BCKDK deficiency was first described by Novarino et al.1in 2012 as a Mendelian form of autism with intellectual disability and epilepsy
- In this first article, six patients were reported (age range: 5 to 22 years)
- Autism and intellectual disability were constant symptoms in all patients

BCKD KINASE DEFICIENCY

- Half had seizures
- All exhibited low plasma levels of BCAA
- In 2014, two new cases with novel genetic variants and a similar phenotype were described

Study 2018-2021

- Twenty-one patients (57% male) from 13 different families with (likely) pathogenic BCKDK variants were included
- Mean age of diagnosis was 5.8 years (range 8 months–16.6 years)

Clinical presentations

Table 1 BCKDK phenotype at diagnosis

Phenotype	HPO code	Frequency *n* (%)
Progressive microcephaly	HP:0000253	17/20 (85)
Global developmental delay	HP:0001263	21 (100)
Motor delay	HP:0001270	21 (100)
Language impairment	HP:0002463	17 (100)
Intellectual disability	HP:0001249	16 (100)
Intellectual disability, severe	HP:0010864	15/16 (93.8)
Developmental regression	HP:0002376	5/8 (62.5)
Behavioural abnormality	HP:0000708	20/21 (95.2)
Autistic behaviour	HP:0000729	14/19 (73.7)
Autism	HP:0000717	11/19 (58)
Self-injurious behaviour	HP:0100716	5/17 (28)
Aggressive behaviour	HP:0000718	8/18 (44.4)
Hyperactivity	HP:0000752	5/21 (23.8)
Restlessness	HP:0000711	6/21 (26.8)
Attention deficit hyperactivity disorder	HP:0007018	4/18 (22.2)
Seizure	HP:0001250	9/21 (42.9)
Bilateral tonic–clonic seizure	HP:0002069	3/18 (16.7)
Generalized myoclonic seizure	HP:0002123	1/18 (5.6)
Typical absence seizure	HP:0011147	2/18 (11.1)
Generalized-onset seizure	HP:0002197	9/21 (42.9)
Focal-onset seizure	HP:0007359	1/21 (4.8)
Interictal epileptiform activity	HP:0011182	12/18 (66.7)
Hypotonia	HP:0001252	5/17 (29.4)
Abnormality of movement	HP:0100022	3/20 (15)
Dystonia	HP:0001332	2/10 (10)
Ataxia	HP:0001251	1/20 (5)
Hyperkinetic movements	HP:0002487	1/20 (5)
Clumsiness	HP:0002312	12/15 (80)
Feeding difficulties	HP:0011968	5/20 (25)

Clinical presentations

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Ataxia	HP:0001251	1/20 (5)
Hyperkinetic movements	HP:0002487	1/20 (5)
Clumsiness	HP:0002312	12/15 (80)
Feeding difficulties	HP:0011968	5/20 (25)
Sensorineural hearing impairment	HP:0000407	3/21 (14.3)
Hyperreflexia	HP:0001347	5/17 (29.4)
Polyneuropathy	HP:0001271	2/17 (11.8)
Abnormal facial shape	HP:0001999	10/21 (47.6)
Full cheeks	HP:0000293	4/21 (19)
Thin upper lip vermilion	HP:0000219	4/21 (19)
Abnormal nasal bridge morphology	HP:0000422	2/21 (9.5)
Hypoplastic philtrum	HP:0005326	2/21 (9.5)
Small forehead	HP:0000350	3/21 (14.3)
Coarse hair	HP:0002208	1/17 (5.9)
Dry skin	HP:0000958	2/17 (11.8)
Inflammatory abnormality of the skin	HP:0011123	3/17 (17.6)
Hydronephrosis	HP:0000126	1/17 (5.9)

Clinical status before treatment

- HC and nutritional status:
- The majority of the patients were born at term (19/21) and all had BW, OFC and length>−2 SD for GA
- At the time of the diagnosis all of them presented a decrease in the OFC score and 16/20 (80%) patients had microcephaly (OFC<−2 SD)
- At diagnosis, 17/18 had BMI Z-scores within the normal range

Neurodevelopmental and behavioural findings

- Global developmental delay :all patients
- All 17 patients older than 2 years of age had language impairment and nine were non-verbal at diagnosis
- The delayed motor milestones :all patients
- Nineteen of 21 patients : gross motor function impairment

PATHOPHYSIOLOGY

- A completely active BCKD might promote an imbalance in the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter GABA,which might help explain neurological phenotype

Neurodevelopmental and behavioural findings

- Sixteen of 16 had intellectual disability

- In all patients except a single case , behaviour issues were noted: 12/17 (70%) fulfilled the DSM-5 criteria of autism spectrum disorder

Cerebral MRI findings

- Cerebral MRI before diagnosis was reported as normal in 11 of 19 patients
- The eight remaining patients had non-specific findings:
- Thin corpus callosum (two), corpus callosum agenesis (two)
- Reduced volume of supratentorial brain parenchyma (one)

Cerebral MRI findings

- Reduced white matter volume (two), enlarged ventricles (two)
- Delayed subcortical and temporal lobe myelination (two)

Biochemical results before treatment

- At diagnosis, the average between BCAA concentrations (average of two samples per patient) was below the reference ranges both in plasma and CSF
- In P19 Val and Leu levels were normal but isoleucine concentration was decreased
- In P20, Leu and Ile (P20) determinations were at normal levels but valine concentration was decreased

Diet therapy and outcome measures

- BCAA supplementation and high total protein intake
- The BCAA treatment observational period was median 3.26 years (0.5–10.7 years)
- The mean Leu, Val and Ile supplementation started at diagnosis was 100 mg/kg/ day

Diet therapy and outcome measures

- BCAA supplements were administered mean 3.6 times per day (range: 3–6).
- At follow-up, natural protein and BCAA supplementation were increased to 2.7 g/kg/day (2–4 g/kg/day) and 206 mg/kg/ day (140–2000), respectively, and distributed four times per 24 h

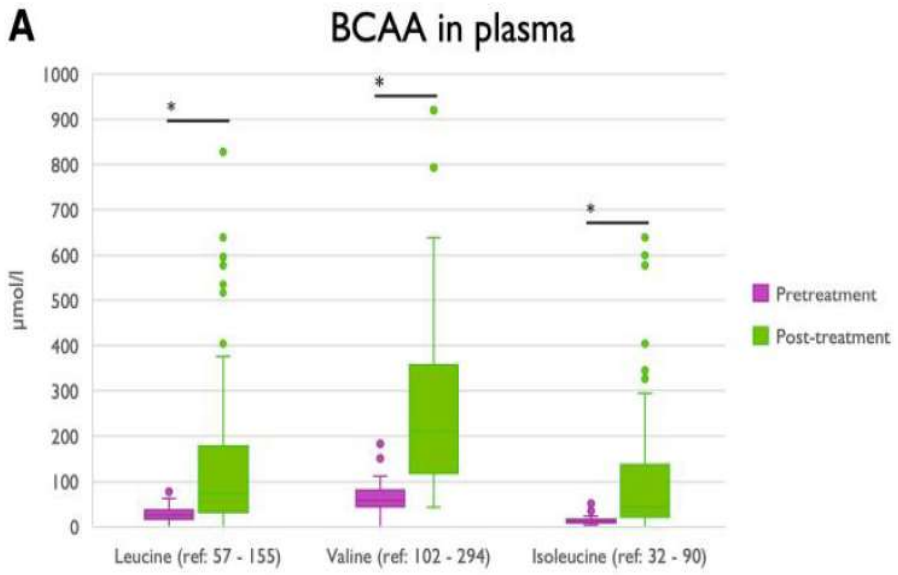
Diet therapy and outcome measures

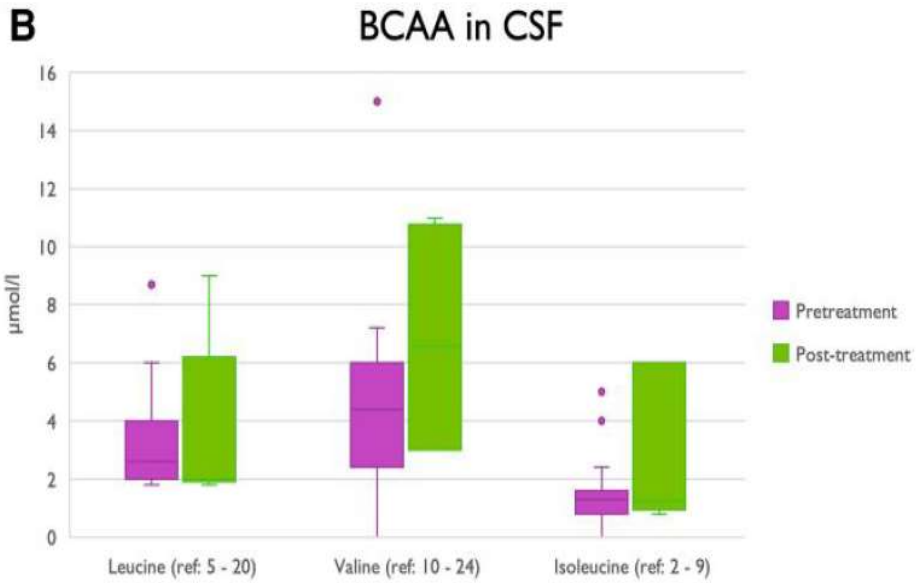
- The Leu:Val ratio was 2:1
- Leu:Ile ratio was 2:1
- After treatment, plasma Leu, Val and Ile increased significantly ($P < 0.001$)

Diet therapy and outcome measures

- The plasma BCAA concentration was under the reference range before the BCAA intake, showing the highest concentrations 2 h after the meal
- Within 3 and 5 h after the meal, Leu and Ile had returned below reference levels

BCAA before BCAA supplementation and a follow-up





Anthropometrics, language, neurodevelopment and behavioural issues

- At follow-up, 11 of 15 patients increased or stabilize their OFC Z-scores.
- Most patients (10 of 12) maintained BMI Z-scores within the normal range at follow-up
- In three patients language improvement was reported after treatment

Anthropometrics, language, neurodevelopment and behavioural issues

- Patients with the earliest treatment introduction developed verbal language and sentence- building acquisition
- Patients who started treatment before 2 years of age did not develop autistic features over time (at the moment all of them are older than 3 years)

Anthropometrics, language, neurodevelopment and behavioural issues

- Most patients did not modify behavioural abnormalities (hyperactivity, restlessness, aggressiveness) with the diet
- Motor functions improved in 8/13 and stabilized in 5/13 patients
- Several patients, in particular those with early treatment, developed gait and fine motor functions
- After BCAA treatment, hyperkinetic movements characterized by very energetic and sudden jerks appeared in one patient

Anthropometrics, language, neurodevelopment and behavioural issues

- Three of nine patients reported persistence of seizures after diet treatment and one patient had the first episode of generalized tonic–clonic seizures one month after onset of treatment

BCKDK-deficient case scores (n=7) entered into the BCKDK post-analytical interpretive CLIR tool

Patient (number)	Sample age (h)	BW (g)	ALA (DBS µmol/l)	VAL (DBS µmol/l)	XLE (DBS µmol/l)	Case score[a]	Percentile rank score of all BCKDK	Interpretation
Spain (15)	48	2600	368 (134–473)	50 (64.7–227)	36 (73.5–228)	412	100	Very likely
Norway (11)	63	1700	351 (174–488)	44 (76.2–243)	38 (84–239)	371	92	Very likely
Germany (2)	61	3670	386 (181–412)	82 (<324)	69 (<294)	62[b]	21	Possibly
Germany (3)	43	4040	366 (181–412)	38 (<207)	41 (<281)	277[b]	100	Very likely
Belgium (16)	72	3200	317 (130–358)	44 (65.2–200)	89 (131–253)	0	—	Not informative zero score[c]
Belgium 2 (17)	72	3200	400 (130–358)	47 (65.2–200)	84 (131–253)	214	57	Likely
Belgium 3 (18)	96	3600	312 (130–358)	81 (65.2–200)	210 (131–253)	0	—	Not informative zero score[c]

CONCLUSION

- Main features:
- Prominent impaired cognitive function
- Autistic traits
- Abnormal motor development
- Epilepsy
- Head circumference stagnation

CONCLUSION

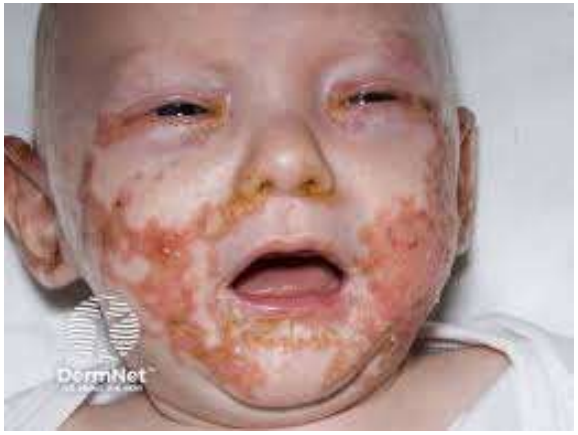
- Marked difference in clinical outcome depending on whether BCAA supplementation occurred :
- early development (before 2 years old) or at later stages (beyond 2 years of age)

CONCLUSION

- HC and motor function were the two main items that improved with treatment.
- Cognition and neuropsychiatric features did not improve after treatment
- Patients who initiated treatment before 2 years of age did not develop autism over time

CONCLUSION

- One interesting feature :acrodermatitis enteropathica-like eczema



CONCLUSION

- In normal conditions, BCAA plasmatic concentration fluctuates significantly before, during and after meals
- Suggesting that frequent feeding is necessary to obtain sufficient levels of BCAA available to the brain
- In fact, BCAA dosage, frequency and formula composition in Leu:Val and Leu:Ile ratios may play a crucial role

CONCLUSION

- Diet with increased natural protein 3–4 g/kg/day and BCAA supplementations (Leu:Val 2:1 and Leu:Ile 2:1)
- Patients here reported had around 200:150 mg/kg/day divided into 4–6 intakes per day
- In any case, it should be adapted depending on the levels achieved in every patient

CONCLUSION

- Enteral BCAA feedings or continuous drip during night could be a neuroprotective strategy during infancy, but may be challenging to sustain in practice
- We propose NBS pilot studies enabling early detection and treatment as the first step to improve outcome in parallel with development of more effective treatments

BRANCHED-CHAIN AMINO ACID TRANSPORTER DEFICIENCY

- Isoleucine, leucine, and valine are transported across the BBB mainly by the heterodimeric LNAA transporter
- A defect in LAT1 caused by pathogenic variants in SLC7A5 results in
- Low brain concentrations of isoleucine, leucine, and valine
- Patients with this defect may present clinically similar to BCKDK-deficient patients

- Autism, microcephaly, gross motor delays, and in some cases, seizures

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