PG-9

メタボローム解析による尿中ザルコシン高排泄の病態解析

Pathological interpretation of elevated excretion of urinary sarcosine by metabolomics

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Background and objectives

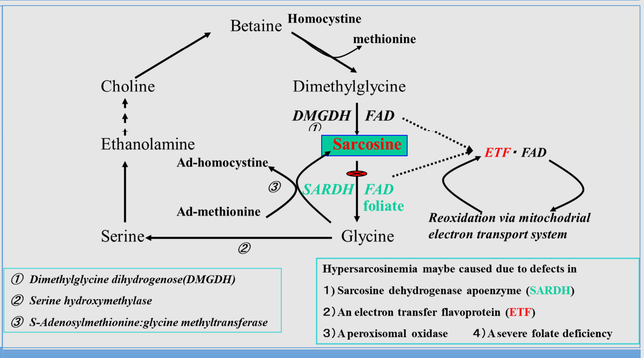
Hypersarcosinemia is an autosomal recessive genetic disorder caused by a deficiency in the enzyme sarcosine dehydrogenase (SARDH). The clinical presentation is multifactorial, with some cases manifesting developmental delay or seizures while others are recognized as benign disorder without specific symptoms.

The cause of high excretion of sarcosine in urine is not due to a single factor, but it plays a role in the following 4 pathways such as -

1. SARDH deficiency
2. Electron transfer flavoprotein(ETF) defect
3. Peroxisomal oxidase deficiency
4. Severe folic acid deficiency

In the clinical course of patients excluding SARDH deficiency, as in case of other 3 conditions, there are many neurological symptoms and developmental disorders and it is therefore important to analyze the pathological conditions when the levels of sarcosine increase in high-risk children.

Hypersarcosinemia & one-carbon cycle



① Dimethylglycine dihydrogenose(DMGDH)
② Serine hydroxymethylase
③ S-Adenosylmethionine:glycine methyltransferase

Hypersarcosinemia maybe caused due to defects in
1) Sarcosine dehydrogenase apoenzyme (SARDH)
2) An electron transfer flavoprotein (ETF)
3) A peroxisomal oxidase　4) A severe folate deficiency

Study Method

Subject ：In high-risk screening of 469,977 patients from China and India over the past 25 years, there are 25 cases had high excretion of sarcosine in urine, in comparison with the age-matched controls

Study point

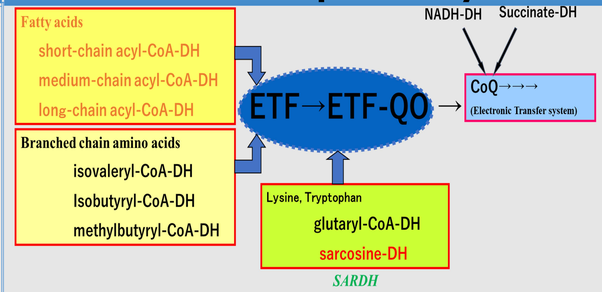
Sarcosinuria only or along with below markers-

ETF defect relative glutaric acid, dicarboxylic acids and glycine conjugate elevate

Folic acid deficiency or cobalamin metabolism abnormalities related methylmalonic acidemia on treatment case

Overall Findings of Reanalysis：The clinical information at the time of the request for testing was combined with the course of treatment and the results obtained later from the genetic test. The reanalysis of pathological findings was done again.

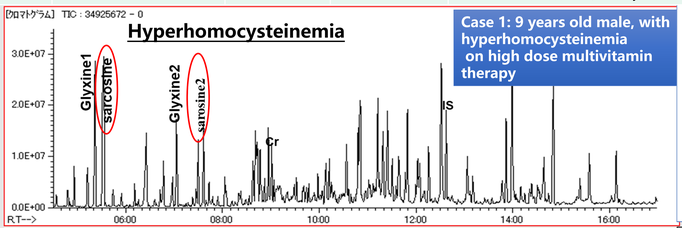
GAII metabolic pathway



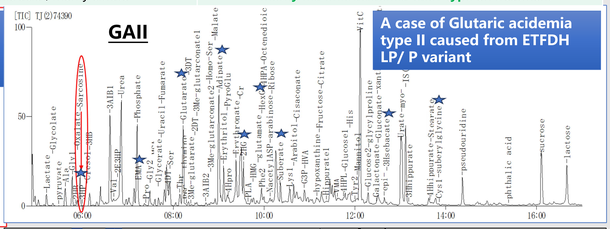
DH1:dehydrogenase, ETF:electron transfer flavoprotein, ETF-QO:ETF-ubiquinone oxidoreductase

Result

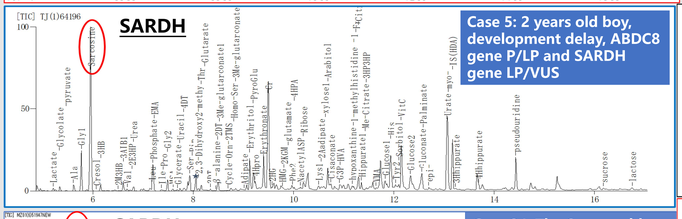
No	Analysis No	Sex	Age	Abnormal metabolites	Clinical information
1	IND9934	M	9Y	sarcosine ↑ glycine, dimethylglycine, methionine high	Bilateral cataract , bilateral optic atrophy, homocystine ↑, on multivitamin therapy with high dose
2	MILS-633	M	9 yrs	sarcosine ↑ some kind organic acid shown slightly increased	IEM?
3	MILS-653	F	7 Months	sarcosine ↑	IEM?
4	MILS-3562	M	10 Years	sarcosine ↑	IEM?
5	TJ64196	M	2Y	sarcosine ↑	Asymmetrical movement of both limbs, developmental delay neonatal diabetes suspicious. SARDH gene and ABCC8 gene
6	TJ889	M	4Y	sarcosine ↑	Developmental delay, autism, hyperactivity.
7	TJ24834	M	1 Y6M	sarcosine ↑	IEM?
8	BMN78263	M	4Y4M8D	sarcosine ↑	IEM?
9	BMN73487	F	9Y3M13D	sarcosine ↑	IEM?
10	BMN70199	M	0Y3M21D	sarcosine ↑	Pneumonitis, malnutrition, developmental delay, dystonia
11	MZ01-36386	F	7Y8M0D	sarcosine ↑	IEM?
12	MZ01-28712	F	1Y2M19D	sarcosine ↑	Convulsion, dystonia, hepatosplenomegaly, developmental delay
13	BCH6978	F	2Y0M20D	sarcosine ↑	IEM?
14	BCH19318	F	2Y9M2D	sarcosine ↑	IEM?
15	BM5015	F	2Y7M	sarcosine ↑	IEM?
16	BM14167	M	4Y6M	sarcosine ↑	IEM?
17	BMN47870	F	6Y	sarcosine ↑	IEM?
18	MZ02-00507	F	20D	sarcosine ↑	convulsion
19	MZ02-02883	F	1Y9M27D	sarcosine ↑	developmental delay
20	MZ02-23896	M	3Y2M22D	sarcosine ↑	IEM?
21	MZ02-25958	M	4Y0M8D	sarcosine ↑	IEM?
22	MZ02-31752	F	10Y3M1D	sarcosine ↑	IEM?
23	MZ01-40749	M	6Y5M28D	sarcosine ↑	IEM?
24	MZ01-52117	M	6Y2M23D	sarcosine ↑	aseptic encephalitis, SARDH gene VUS/VUS
25	TJ68967	F	11M	sarcosine ↑ methylmalonic acid , methylcitrate	methylmalonic acidemia Cbc1 type on treatment



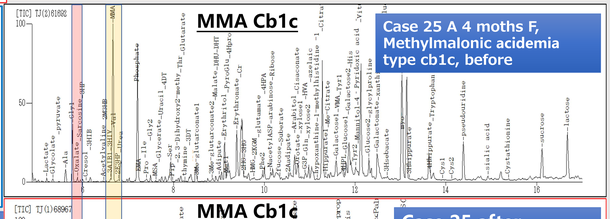
Case 1: 9 years old male, with hyperhomocysteinemia on high dose multivitamin therapy



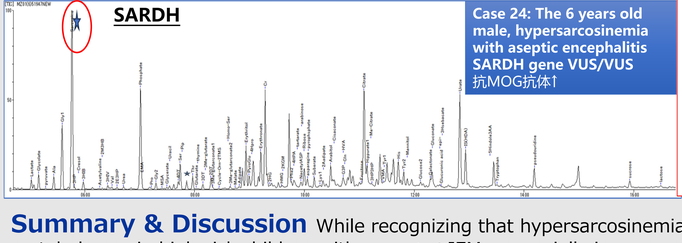
A case of Glutaric acidemia type II caused from ETFDH LP/ P variant



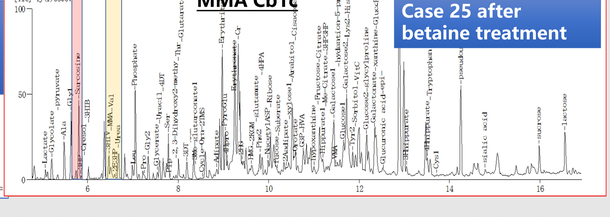
Case 5: 2 years old boy, development delay, ABDC8 gene P/LP and SARDH gene LP/VUS



Case 25 A 4 moths F, Methylmalonic acidemia type cb1c, before



Case 24: The 6 years old male, hypersarcosinemia with aseptic encephalitis SARDH gene VUS/VUS
抗MOG抗体↑



Case 25 after betaine treatment

Summary & Discussion While recognizing that hypersarcosinemia is a benign disease, care should be taken when analyzing the metabolomes in high-risk children with suspected IEMs, especially in cases of high excretion of sarcosine, ETF abnormalities, peroxisomal oxidase deficiency, folate deficiency and the pathology of betaine treated patient.

本発表演題に関連して開示すべきCOI関係にある企業などはありません。