Genomics & A Medical Home

Approach to Care for Patients with Metabolic Disorders

What is a Medical Home for Child or Adult with a Metabolic Disease?

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In 1986-1988, my fellowship years, the 6 physicians at CHOP who specialized in *Biochemical Genetics* followed 150 patients - total. Richard Kelley provide general pediatric care for 87 of these cases.

The 6 physicians at CHOP cared for 10 Mennonite children with MSUD but no other founder-disorders from the Amish & Mennonite populations of Lancaster County, only 40 miles west of Philadelphia. Victor McKusick started his studies of the Amish in 1963 & published *The Medical Genetic Conditions of the Amish* in 1978.

The first Amish patient I saw as a fellow in Biochemical Genetics was a 4-year-old boy with glutaric aciduria type 1, June 19, 1988.

WERE THESE POPULATIONS "UNDERSERVED?"

Today two pediatricians at the Clinic for Special Children care for over 2000 patients from these populations with 115 different recessive disorders.

Edwin Naylor's *Expanded Newborn Screening Program* using MS/MS started in 1993-94.

In 2012 we follow more than 400 patients from the Plain Communities that were diagnosed through Newborn Screening including:

- >90 Mennonite patients with classical MSUD
- 57 cases of the Amish variant of glutaric aciduria type 1
- 34 children with propionic acidemia
- 42 cases of MCADD
- 20 cases of a severe, but treatable, form of MTHFR deficiency

NEWBORN SCREENING CORE PANEL OF 29 DISORDERS
MENNONITE 6 & AMISH 8

	~ # pts
FATTY ACID OXIDATION DEFECTS	
MCADD (M+,A-)	**42**
VLCAD (M-, A+)	**2**
ORGANIC ACIDEMIAS	
GLUTARIC ACIDURIA TYPE 1 ((M-,A+)	**93**
3-METHYLCROTONYL COA DEFICIENCY (M+,A+)	**30**
PROPIONIC ACIDEMIA (M+,A+)	**34**
AMINO ACID DISORDERS	
PHENYLKETONURIA (M+,A+)	**6**
MAPLE SYRUP DISEASE (M+,A-)	**134**
HOMOCYSTINURIA (M-,A-) (A+ MTHFR)	**22**
TYROSINEMIA TYPE 3 (M-,A-) (M+ Tyr 3)	**8**
CONGENITAL HYPOTHYROIDISM (M+,A+)	**22**
BIOTINIDASE DEFICIENCY (M+,A+)	**6**
CONGENITAL ADRENAL HYPERPLASIA	**30**
21-hydr def)	
3-beta OL,	
Methyl oxidase-2	
CLASSICAL GALACTOSEMIA (M-,A+)	**6**
HEARING LOSS (M+,A+) Many different forms, common problem	
Total	**433**

Other inherited disorder found within the Plain populations for which treatment outcomes justify diagnosis in the pre-symptmatic infant by family targeted carrier testing & newborn testing.

	Patients
Crigler-Najjar disease	24
RBC Pyruvate Kinase Deficiency	30
Cystinuras	25
MTHFR Deficiency	22
Bile Salt Transport/Synthesis Disorders	
TJP2	30
BAAT	10
Byler Disease	6
SCID Syndromes	
CHH RPMR with hypo-immune function	33
IL7 Receptor Defects	10
RAG1 Mutations	10
Adenosine Deaminase Deficiency	2
Nephrotic Syndromes	
Pierson Syndrome with retinal detactment	13
Congenital Nephrotic Syndrome NPHS1 & 2	10
Dopa-responsive dystonia TH mutation	2
TOTAL	227

MSUD - Emergency Admissions to Lancaster General Hospital for Acute Metabolic Care. n=267, 1990-2012

Neonatal presentations **~10%**

Down syndrome VSD repair, congenital bowel obstruction (HMC)
Sepsis SCID (IL7-SCID)
Sepsis & pneumonia Group B Strep
*+Newborn Screens & Illness (34 of 69)**

Infectious illnesses **~78%**

Gastroenteritis (Rotavirus)
Pneumonias (RSV)
Otitis media
Strep pharyngitis
Bacterial/fungal sepsis
Herpes simplex 1 stomatitis

Surgery & Trauma **~12%**

Appendicitis
Hirshsprung Disease with distal colonic resection (HMC)
Cholecystitis
Ovarian torsion & Cyst
Hysterectomy
Fracture femur, skull fracture

**NOTE: 35/69 newborns with MSUD were <24 hrs of age & asymptomatic when diagnosed because of carrier testing or +family history. These infants were managed out-of-hospital.*

Cost Analysis for RotaTeq & No RotaTeq n=100, at LGH

	CSC RotaTeq (n=50)	No RotaTeq (n=50)
Cost of vaccine ($169/patient)	$8,450	$0
Cost of administration	$4,700	$0
Work-Lost	$1,275	$0
Travel cost	$2,700	$0
Total cost of RotatTeq	$17,125	$0
# of infants hospitalized for Rotavirus	1	5
# of days of non-ICU care	5	20
Costs of non-ICU Care ($3,335/day)	$7,003	$66,700
# of ICU days	0	10
Costs of ICU Care ($3,335X2.5=$8338)	$0	$83,380
Direct cost of hospitalization	$7,003	$150,080
Cost of RotaTeq + Hospital	$24,128	$152,833

Hospital cost savings from vaccine **$128,705**

(Based upon Yount LE et al. Pediarics 2004;114;1606-1611)

Patients with many different genetic disorders are at risk for severe illnesses induced by common, seasonal, preventable infections:
Rotavirus, Influenza A&B, Hepatitis A&B, Varicella, Hemophilus Influenza, Pneumococcus, Pertussi, and RSV

Glutaric Aciduria *

Propionic Acidemia*

Crigler-Najjar Disease*

Maple Syrup Urine Disease*

Medium Chain Acyl Dehydrogenase Deficiency

Adrenal Insufficiency Syndromes

Ellis van Creveld with pulmonary hypoplasia

Cartilage hair hypoplasia with pulmonary hypoplsia or immune deficiency

Down Syndrome

Prader Willi Syndrome

Immune Deficiencies

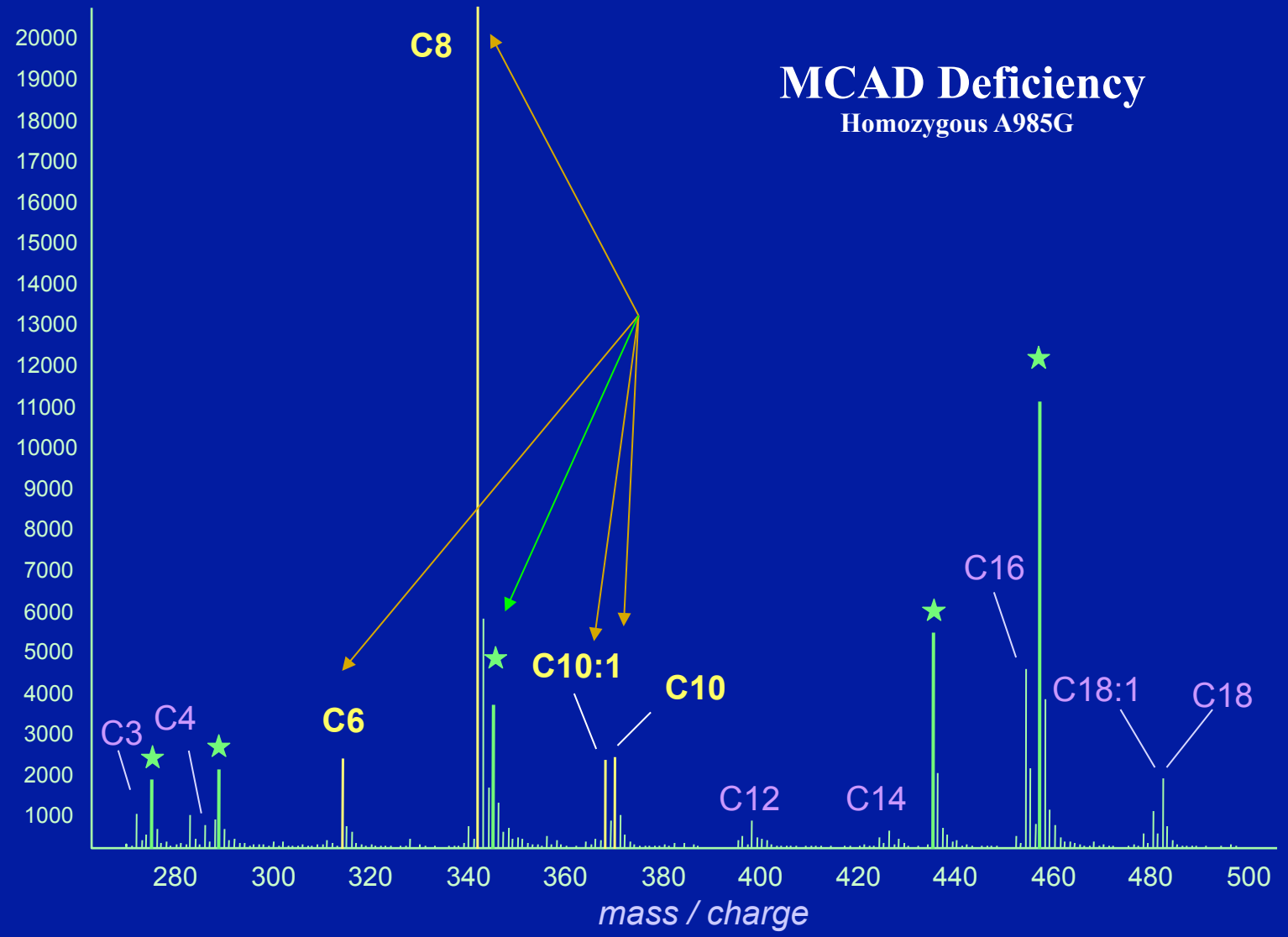
Amish Lethal Myoapthy, Troponin 1 Deficiency

Generalized dystonia, spasticity, and other disabilities

Congenital Heart Disease, many variants

Seizure syndromes, many variants

Diagnosis: MCAD Deficiency



CASE - A 10 day old male infant was referred to me because of a positive neonatal screen for octanoylcarnitine.

Serum and urine analysis GC/MS in my lab showed increase serum octanoate & cis-4-decenoate, urine hexanoyl & suberylglycine and supported the diagnosis of MCADD.

Molecular tests showed that the parents and the three other healthy children carried the common delta 985 mutation.

A sibling of this child died 16 months before. She was found dead in her crib 18 hours after her first DPT/OPV/H FIu immunization. A Reye-like fatty infiltration of the liver was noted at autopsy, regardless, her death was attributed to SIDS.

MS/MS & molecular studies of her newborn filter paper confirmed that this infant in fact had MCADD. She died a metabolic illness provoked by a respiration tract illness & an immunization, not from SIDS.

What is the immediate cause of these deaths?

FATTY ACID OXIDATION DISORDERS DETECTED in 2,300,000 infants tested.

- MCAD Deficiency 176
- VLCAD Deficiency 37
- LCHAD Deficiency 35
- CPT-II Deficiency 18
- SCAD Deficiency 10

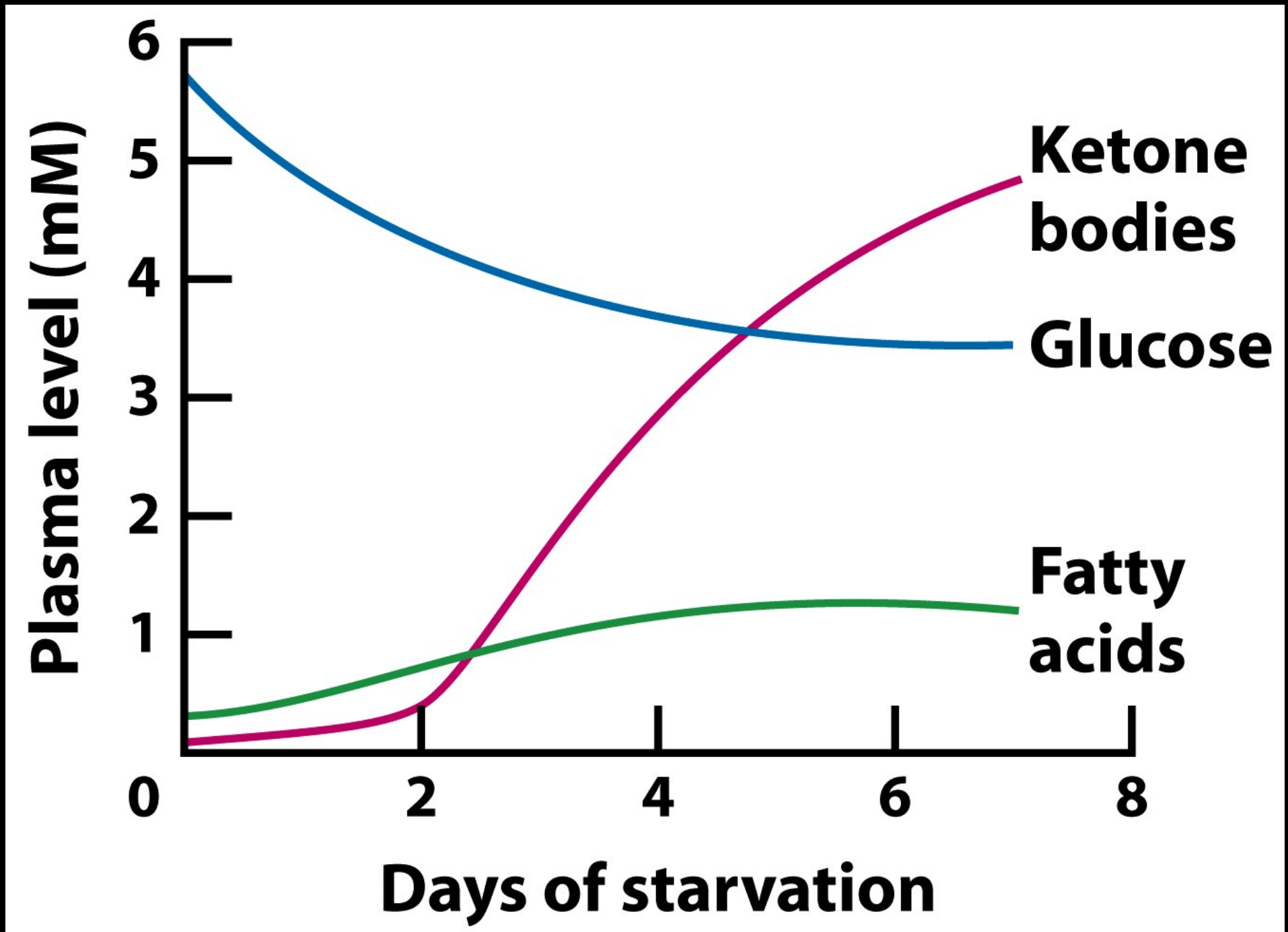


Figure 27-16
Biochemistry, Sixth Edition

Mennonite MSUD 1963-1988

Mortality 11/20 (55%)

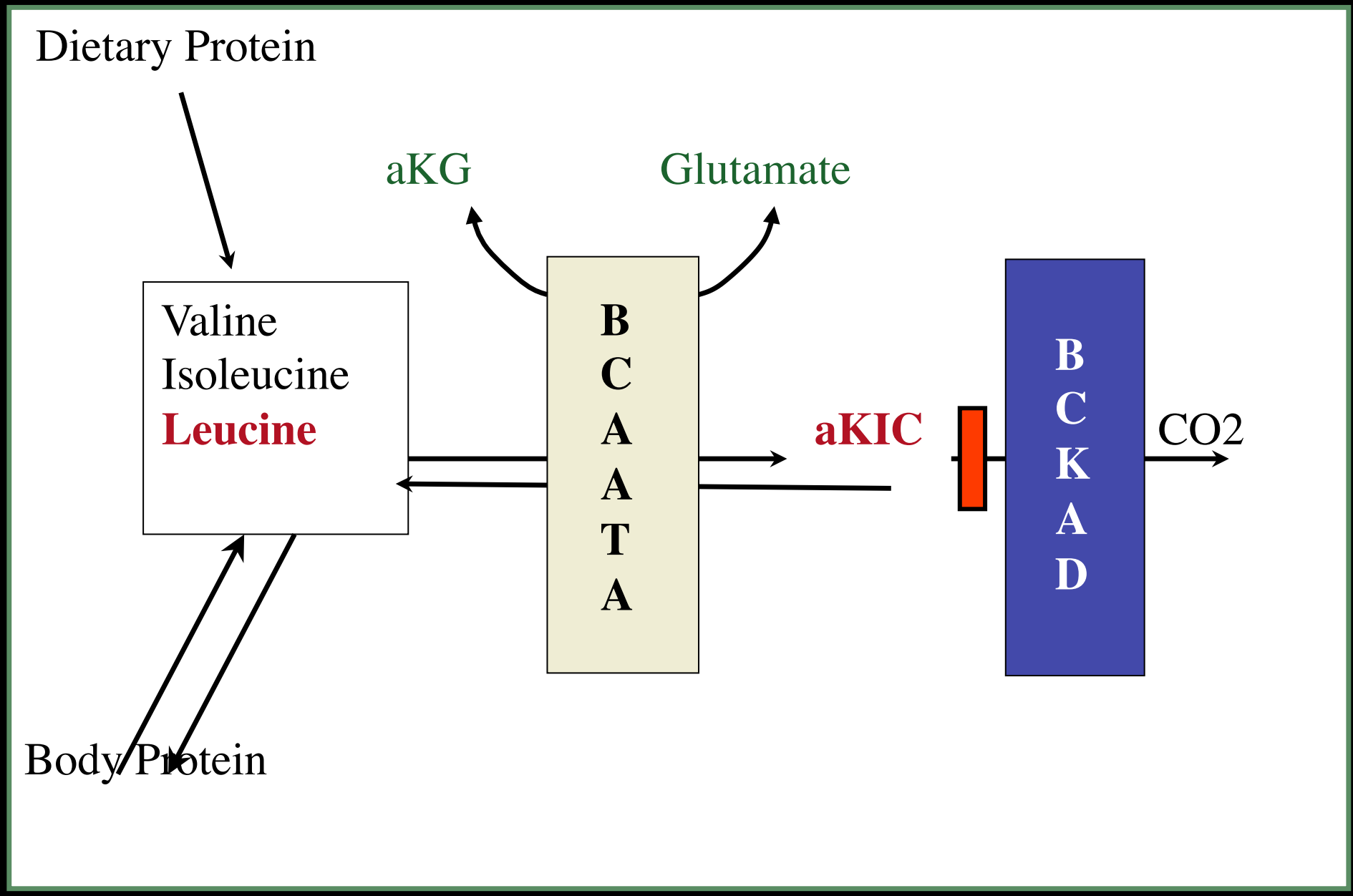
Moderate to Severe Cognitive & Motor Disabilities in 100% of Survivors.

MENNONITE MSUD PATIENTS BORN 1963 - 1984: Mortality from Cerebral Edema 11/20 (55%); Cognitive & Physical Disabilities 100%

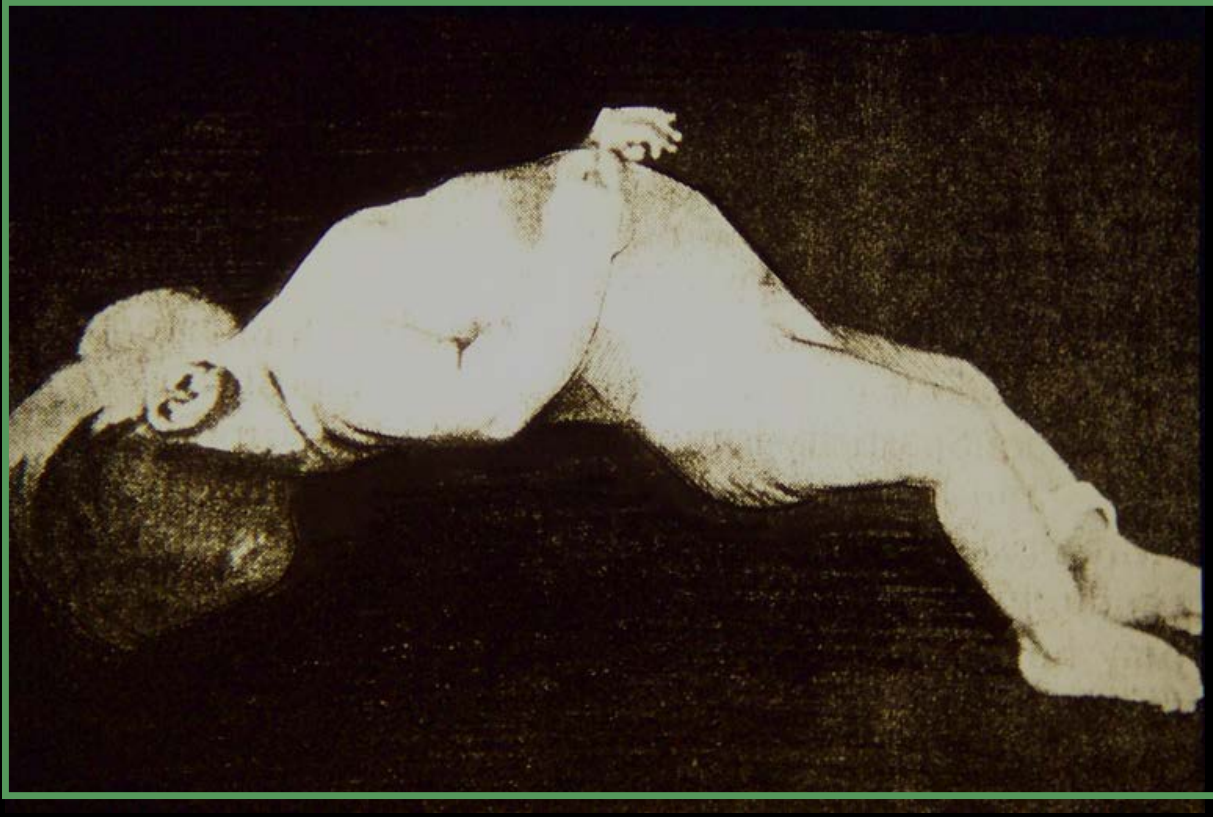
					Clinical Estimate of Disability -SD Below Norm of 0		
Year of Birth	Patient	Age	Age at Death	Illness Provoking Brain Edema	Cognitive & Functional	Physical Disability	Notes
1984	IA Ho	26			-2	-1	moderate cognitive imparementFull Scale IQ 55 & mild motor imparement
1983	MK H	Dead	3 yrs	infection & vomiting			
1982	Da E	Dead	6 yrs	Infection & vomiting			
1980	Mar Z	30			-2	-3	moderate cognitive imparment Fill Scale IQ 57 & severe spasticity
1980	Ne N	31			-3	-2	profound MR, moderate spasticity
1980	Ch Mar	Dead	8 yrs	myocoplasma pneumonia			
1979	Na H	Dead	3 yrs	infection & vomiting			
1979	Ja H	Dead	5 yrs	infection & vomiting			
1978	Ke Mar	33			-2	-1	moderate cognitive imparement & mild motor imparement
1978	A F	33			-2	-1	moderate cognitive imparement & mild motor imparement
1976	El H	Dead	4 mos	infection & vomiting			
1974	Ed H	37			-2	-3	moderate cognitive imparement, good language & memory severe lower extremity spasticity & foot dystonia
1971	Su F	Dead	4 yrs	infection & vomiting			
1970	Me H	Dead	13 days	neonatal illness			
1970	Sh Br	42			-2	-2	moderate cognitive imparement & mild motor imparement
1970	P Ku	42			-3	-2	severe cognitive imparement & mild motor imparement
1967	Le K	45			-3	-3	severecognitive & severe lower extremity spasticity & dystonia
1967	El F	Dead	13 days	neonatal illness			
1965	Mo Br	Dead	9 yrs	infection & vomiting			
1963	Wi F	Dead	3 mos	infection & vomiting			

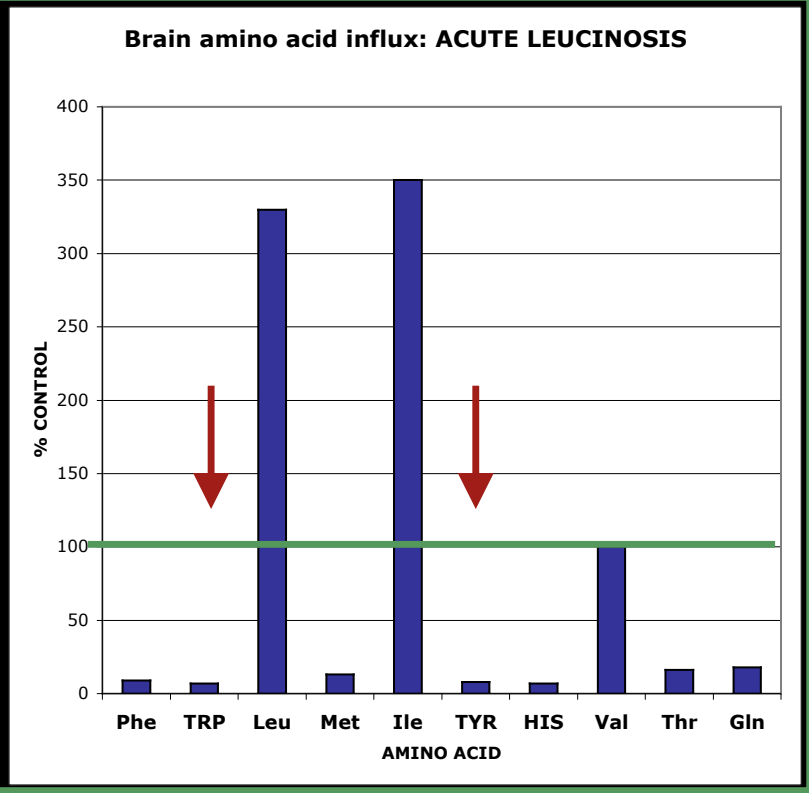
CLASSICAL MAPLE SYRUP DISEASE

Mennonites, homozygous T->A in exon 9 at aa position 1312



Opisthotonus

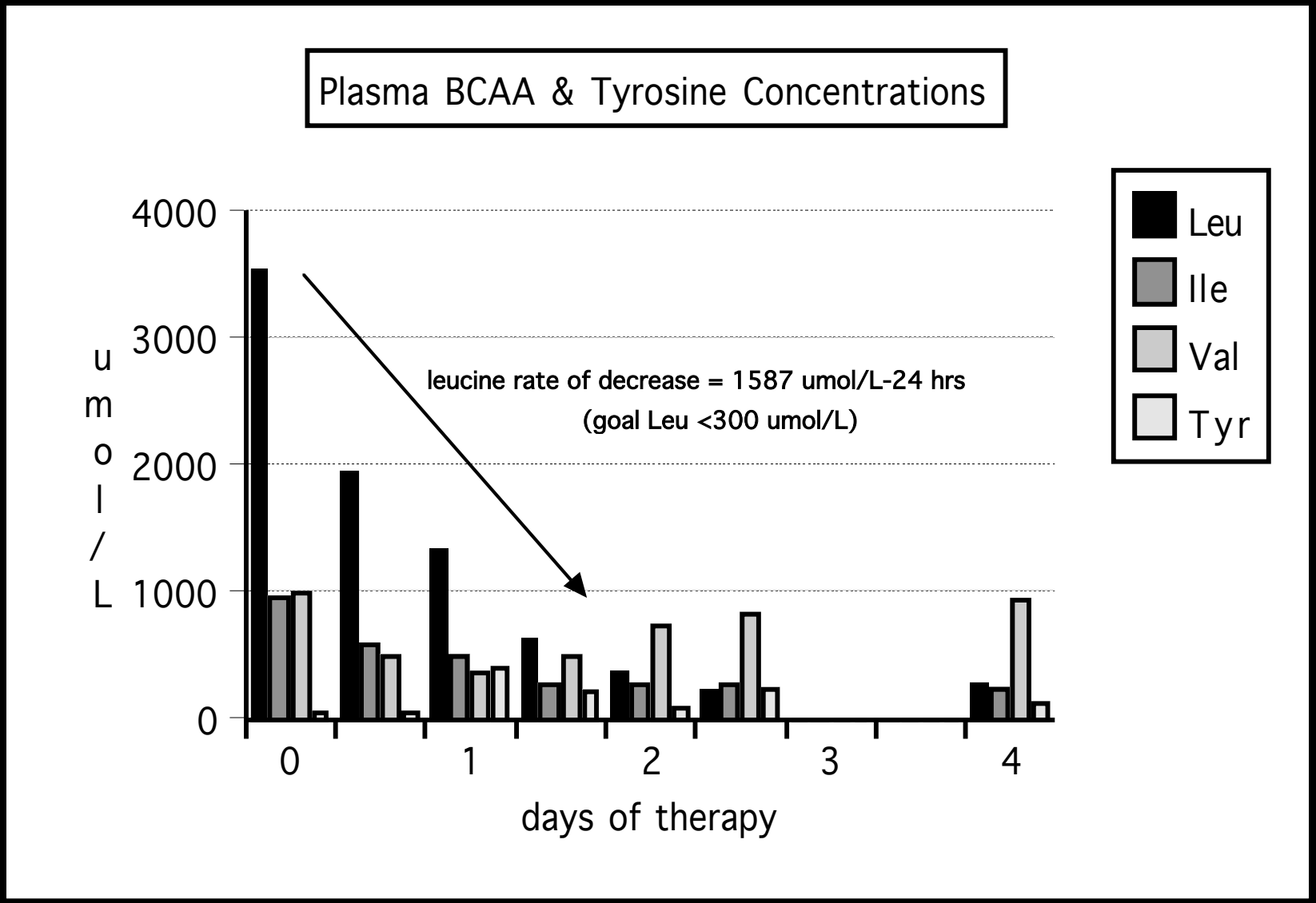




Acute Brain dopamine Deficiency

Acute Brain Serotonin Deficiency

Plasma branched chain amino acids and tyrosine concentrations during the first four days of therapy in an ill neonate with MSUD.



VARIABLES OF PROTEOLYSIS AND PROTEIN SYNTHESIS

	PROTEOLYSIS		PROTEIN SYNTHESIS
	Stimulates	***Inhibits***	***Stimulates***
MUSCLE	Interleukin-6 Interleukin-1 Tumor necrosis factor Prostaglandin E2 Sepsis Starvation Amino acid deficiency Low intracellular Gln Cell dehydration Muscle denervation Cortisol (permissive) Hypoinsulinemia	Glucose ECF amino acids Glutamine uptake Insulin Insulin-like GF-1 Cell hydration	Growth hormone/IGF-1 Intracellular glutamine Intracellular glutamine 8 mM/kg Cell hydration
LIVER	IL-6, IL-1, TNF Glucagon Epinephrine (beta-1) Cell dehydration	Insulin IGF-1 ECF BCAAs + alanine Cell hydration	Insulin Cell hydration

Variables of management of Maple Syrup Urine Disease MSUD-TPN

1. Glucose infusion rate (10-12 mg/kg-min.) & total daily caloric goal (2 x BMR or >) 120-140 Cal/kg-24 hrs with lipid infusion providing 40-50% of total calories.

2. Insulin infusion rate 0.05 – 0.15 units/kg-hr to keep blood glucose 80-140 mg/dl with infusion rate of 10-12 mg/kg-minute.

3. Protein grams/kg as MSUD amino acid mixture, enriched with L1-NAA & conditionally essential AA 2-3 g/kg-24 hrs. Glutamate, Glutamine, and Alanine are given as conditionally essential amino acids ~100-200 mg/kg-24 hrs each).

4. Valine & Isoleucine mg/kg-24 hrs. (60-120 mg/kg-24hrs)

5. Sodium & potassium adequate mEq/kg-24 hrs to replace Na deficit, urine Na/K losses, and maintain a stable serum osmolality. Na+ losses & replacement may be 10-15 mEq/kg-24 hrs; K+ are also increased by furosemide & mannitol diuresis used to control cerebral edema.

Genomics & A Medical Home

A Medical Home is the place where,
when you have to go there,
they have to take you in,
And, they know how to care for you.

D. Holmes Morton MD
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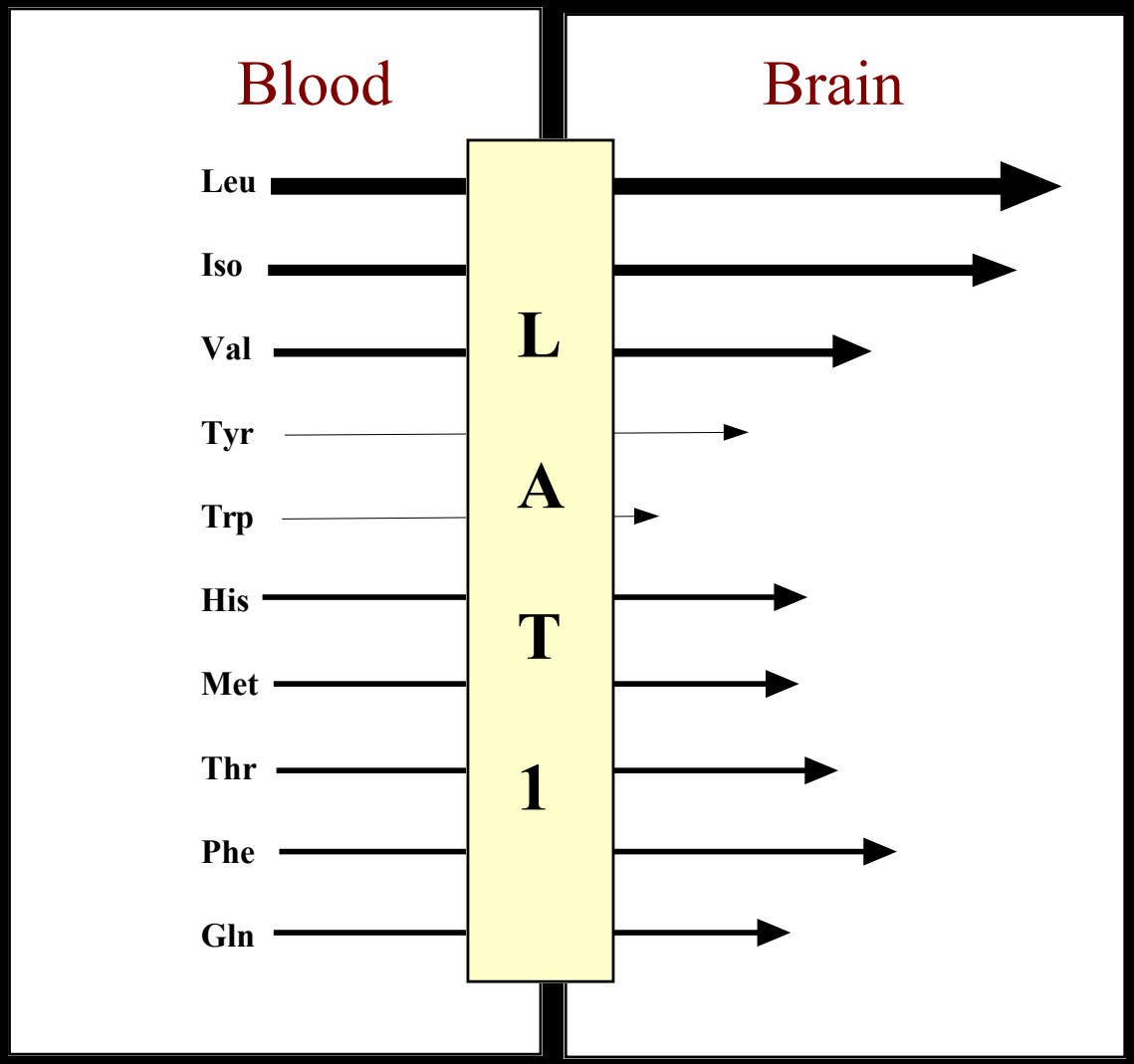
Strasburg, Pennsylvania

Transport Competition & Outcome in MSUD

Chronic amino acid malnutrition & the developing brain



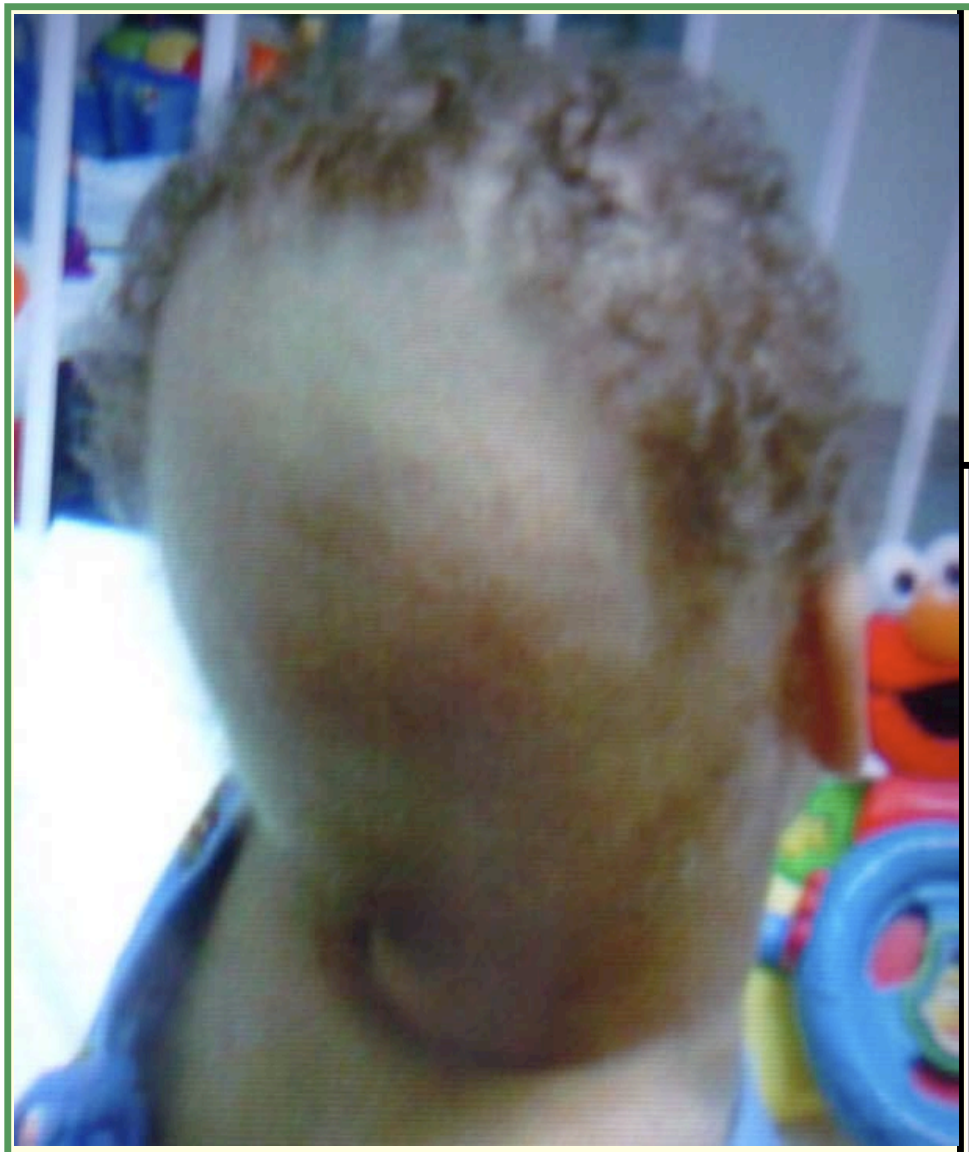
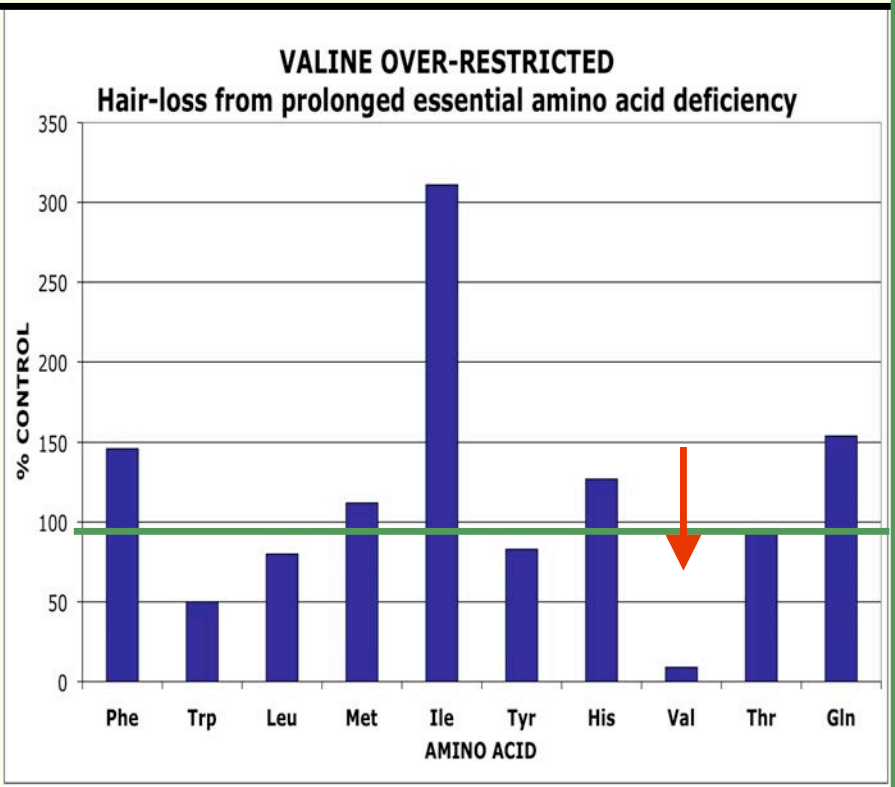


Photo with parental permission

ARRESTED HEAD GROWTH
HYPOMYELINATION
ACRODERMATITIS/HAIR LOSS
NORMOCYTIC ANEMIA
GROWTH FAILURE
IRRITABILITY/ANOREXIA

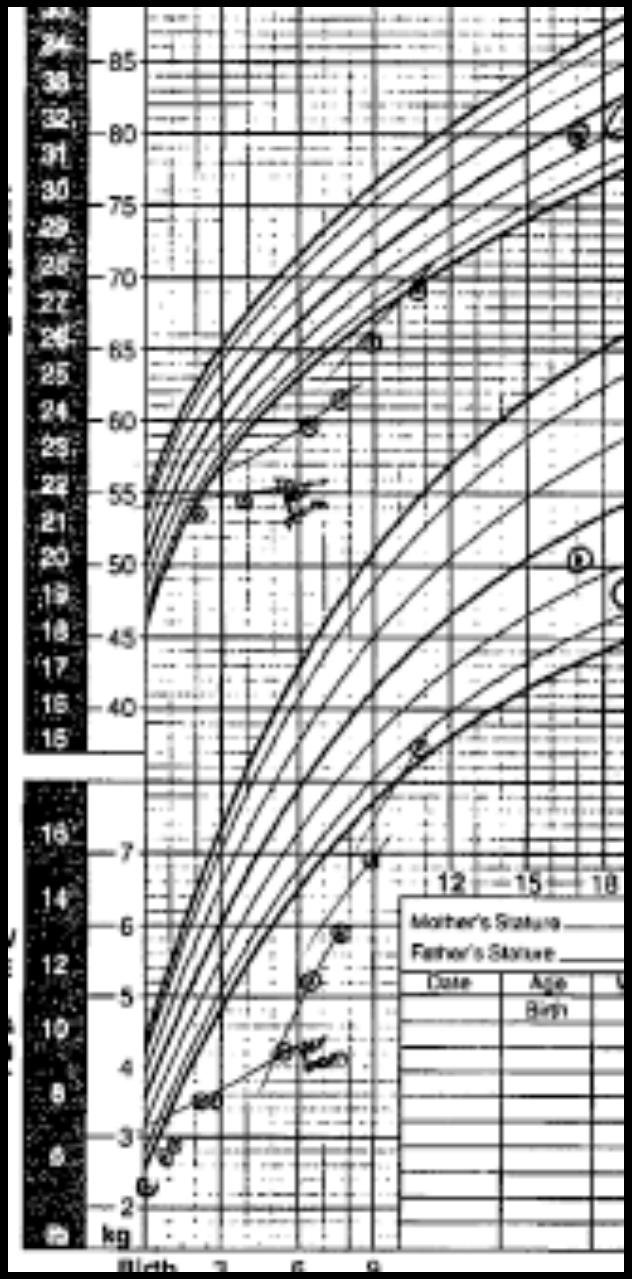


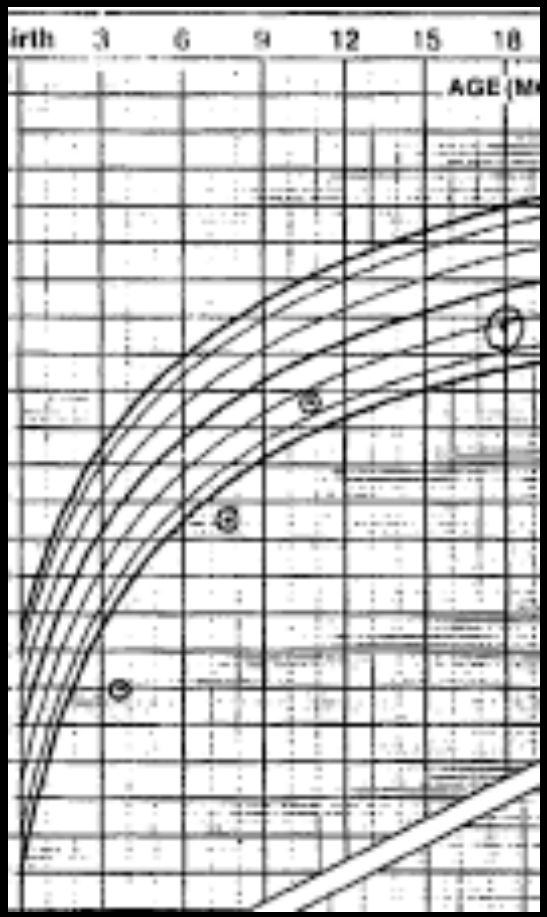
T C:

Poor growth in terms of weight, length & head circumference were the result of prolonged essential amino acid deficiencies during the first 6 months.

The calculated valine uptake into the CNS from birth to 6 months of age was less than 3% of normal – Z-score <-3.3 - over a prolonged period.

This data predicts poor neuro-cognitive outcome as compared to our Mennonite patients who also have a severe MSUD variant.

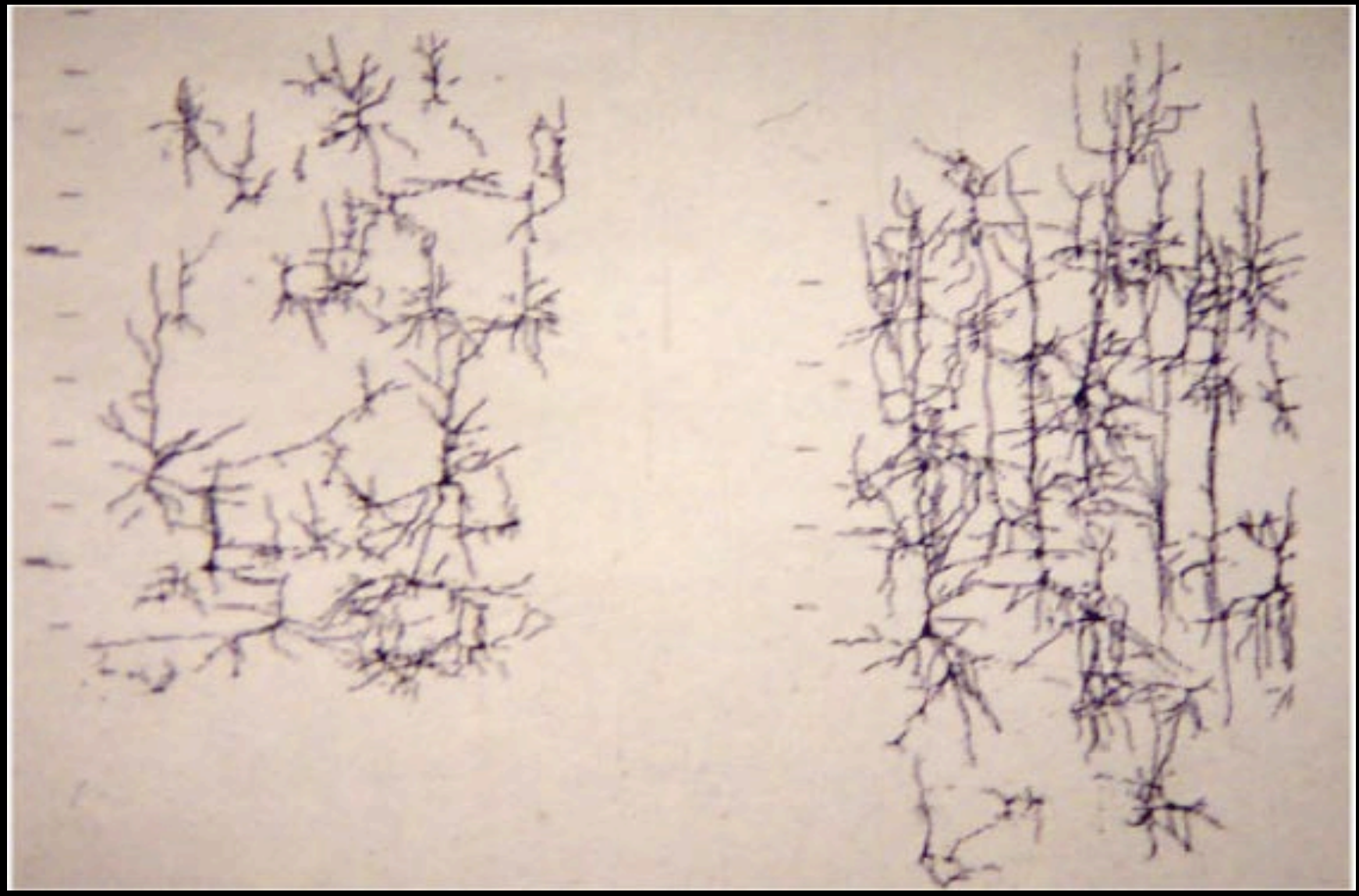




DOB 7/4/2008. Adm. to NICU at age 7-days. Dx with MSUD at 14-days. Discharged age 44 -days. Time until Leucine < 400 uM was 18 days, age 30-days. Leucine intoxication lasted for 4 weeks.

Fine Cortical Branching

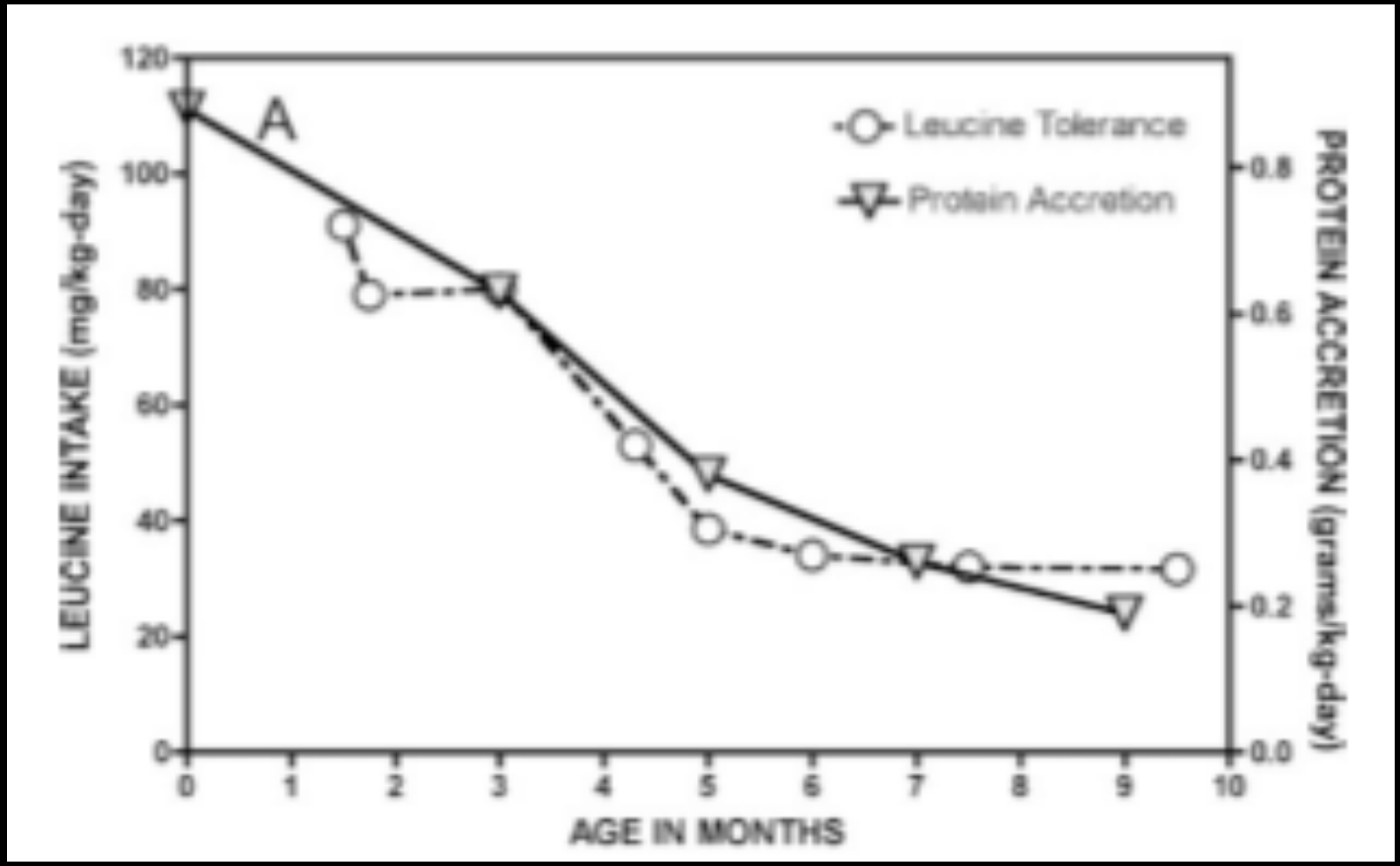
The Neuropathological Correlate of Mental Retardation in Protein Malnourishment Syndromes



MSUD Poorly Treated

Normal

Growth related protein accretion & leucine tolerance related to age in Classical MSUD



T C

On admission to LGH his prescribed Leucine intake at 33 months 55 mg/kg-day, all from 8 oz of cow's milk. Isoleucine 34 & Valine 37 mg/kg

.

No supplements of Ile or Val were being used to prevent deficiencies.

Ketonex-2 provided 36 grams of protein as free amino acids.

Profree formula provided additional calories to total 93 Cal/kg-day.

Parents did not have a sick day protocol. No monitoring was done to detect increases in leucine caused by common illnesses. No adjustments in leucine intake were made when a high leucine or when isoleucine or valine deficiency was found.

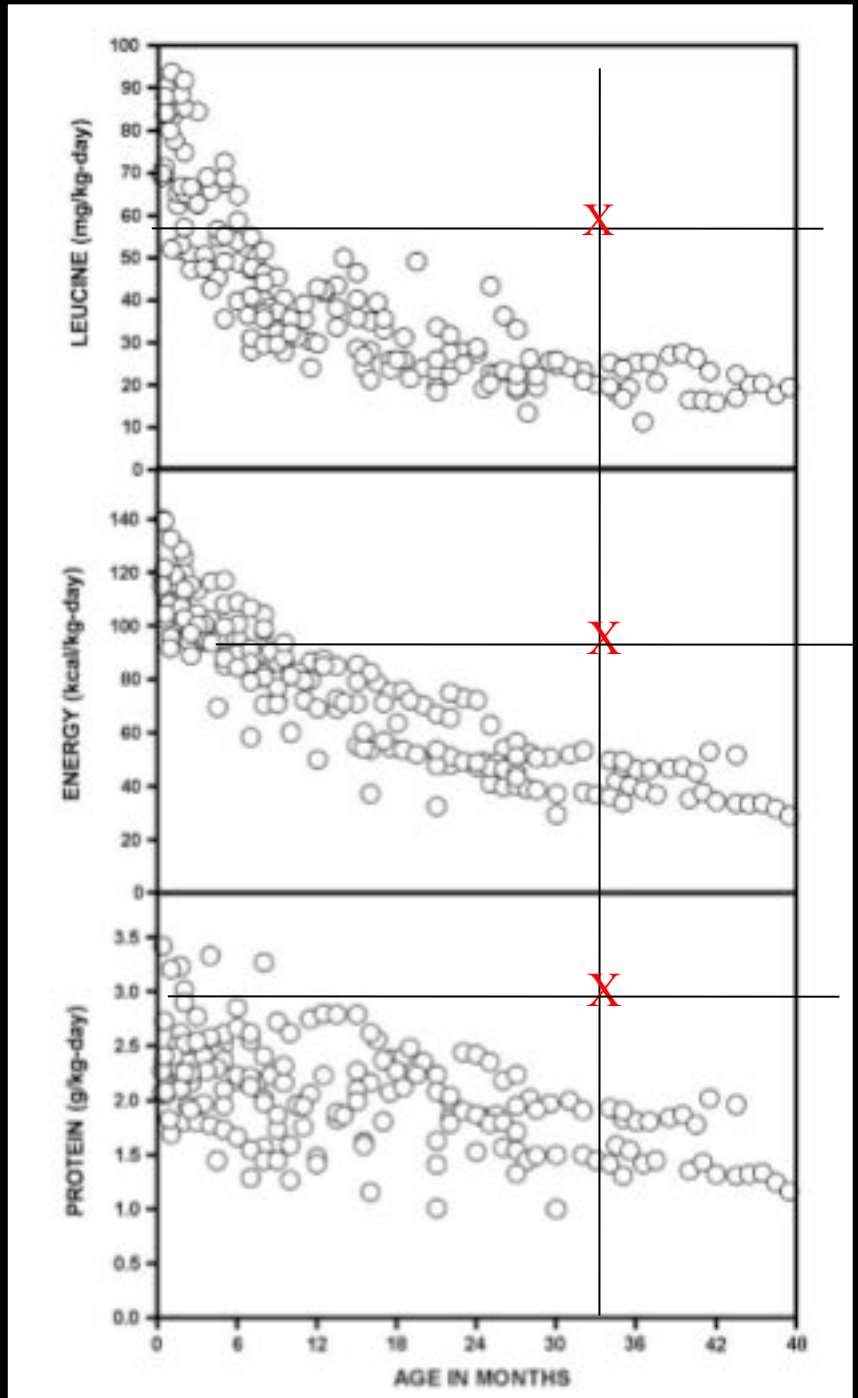


Fig. 3. Serial leucine, energy, and protein intakes of 15 Mennonite infants with MSUD treated with study formula.

TC

On discharge from LGH his prescribed Leucine intake at 33 months 17 mg/kg-day with an expected range of 15-25 mg/kg, all from Similac 20 grams.

Isoleucine 9 mg/kg & Valine 17 mg/kg
Supplements of Ile 0, Val 10 ml 100mg. To be adjusted as needed based upon weekly amino acid results.

Applied Nutrition MSUD Complex Jr. 185 grams provided 2 gm/kg-day as amino acids.

Total Caloric intake 74 Cal/kg-day.

Calculated BMR 37 Cal/kg-day, 2 X BMR = 74 Cal/kg-day.

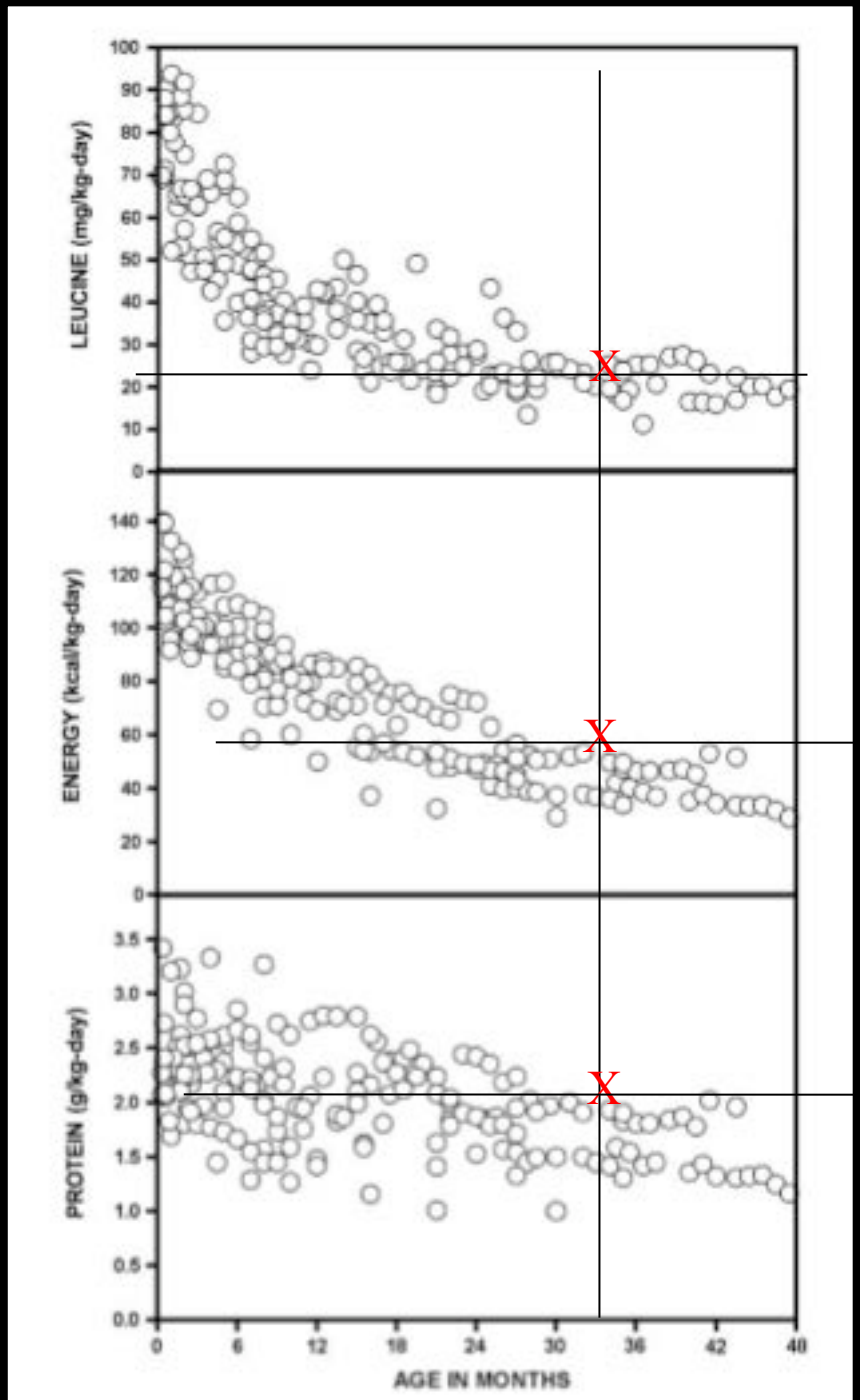
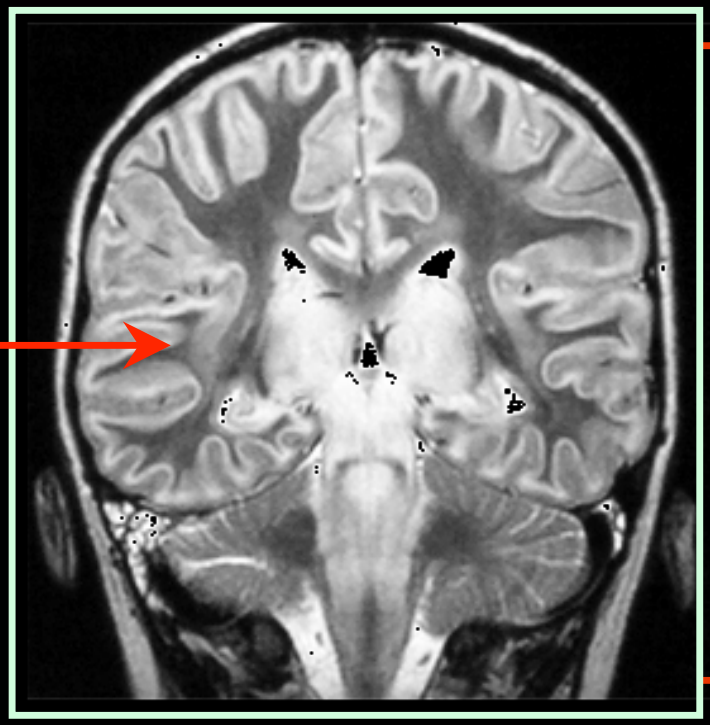


Fig. 3. Serial leucine, energy, and protein intakes of 15 Mennonite infants with MSUD treated with study formula.

Leucine
&
KIC



ACUTE INTOXICATION

Vomiting

Hallucinations

Imbalance

Coma

Brain swelling

Stroke or sudden death

CHRONIC PROBLEMS

Arrested brain growth

Developmental delay

Mental retardation

Spastic cerebral palsy

Chronic mental illness

Physical and mental disability

New England Journal of Medicine 1991; 134, 175-179

Vol. 324 No. 3 BRIEF REPORT —

BRIEF R

BRANCHED-CHAIN AMINO ACID–FREE PARENTERAL NUTRITION IN THE TREATMENT OF ACUTE METABOLIC DECOMPENSATION IN PATIENTS WITH MAPLE SYRUP URINE DISEASE

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MARC YUDKOFF, M.D., AND STANTON SEGAL, M.D.

The newborn in this report, Rachel W, was born with the severe Mennonite variant of MSUD in November of 1989. (Case #33 in Morton 2002) She was the first infant from the Lancaster County population to be managed with MSUD-parenteral nutrition. She has been cared for at the *Clinic for Special Children* for 22 years. Her growth and development were normal. She was an "A" student in school, is now married, and recently underwent a curative liver transplant.

We began using MSUD-parenteral nutrition at LGH in 1990 and have successfully rescued more than 250 ill cases of MSUD. MSUD-PN is

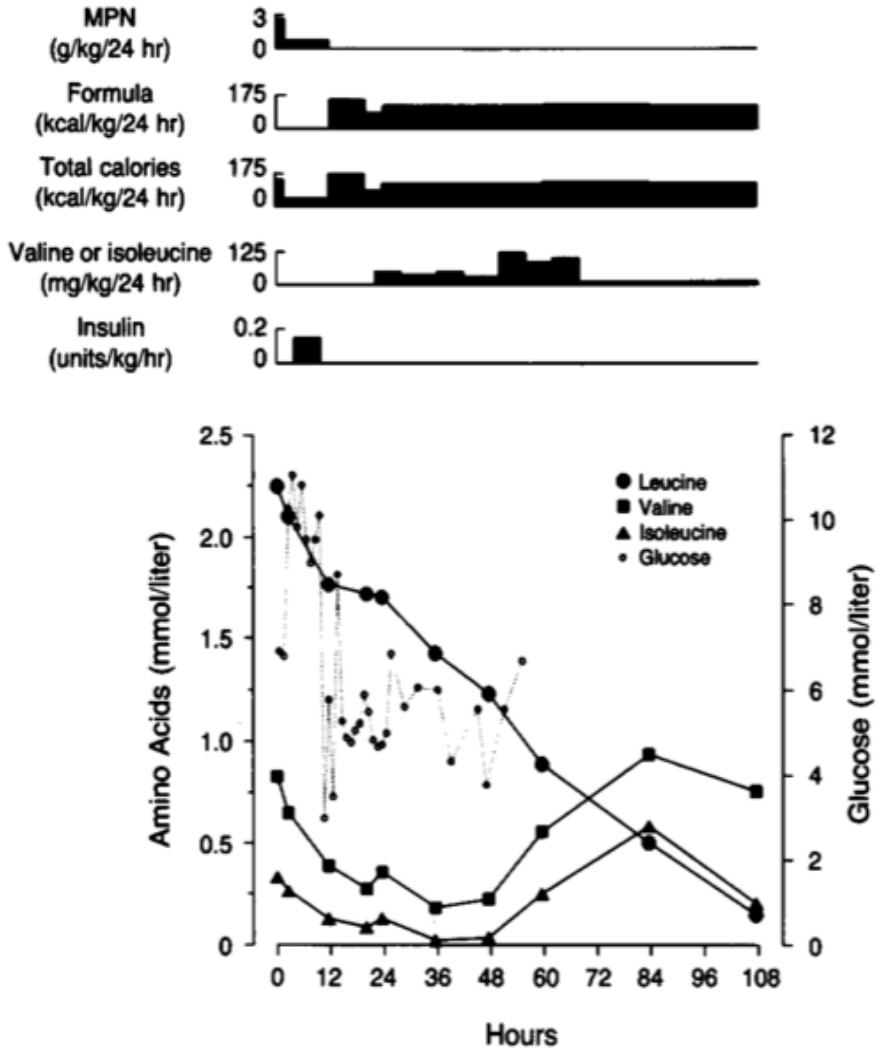
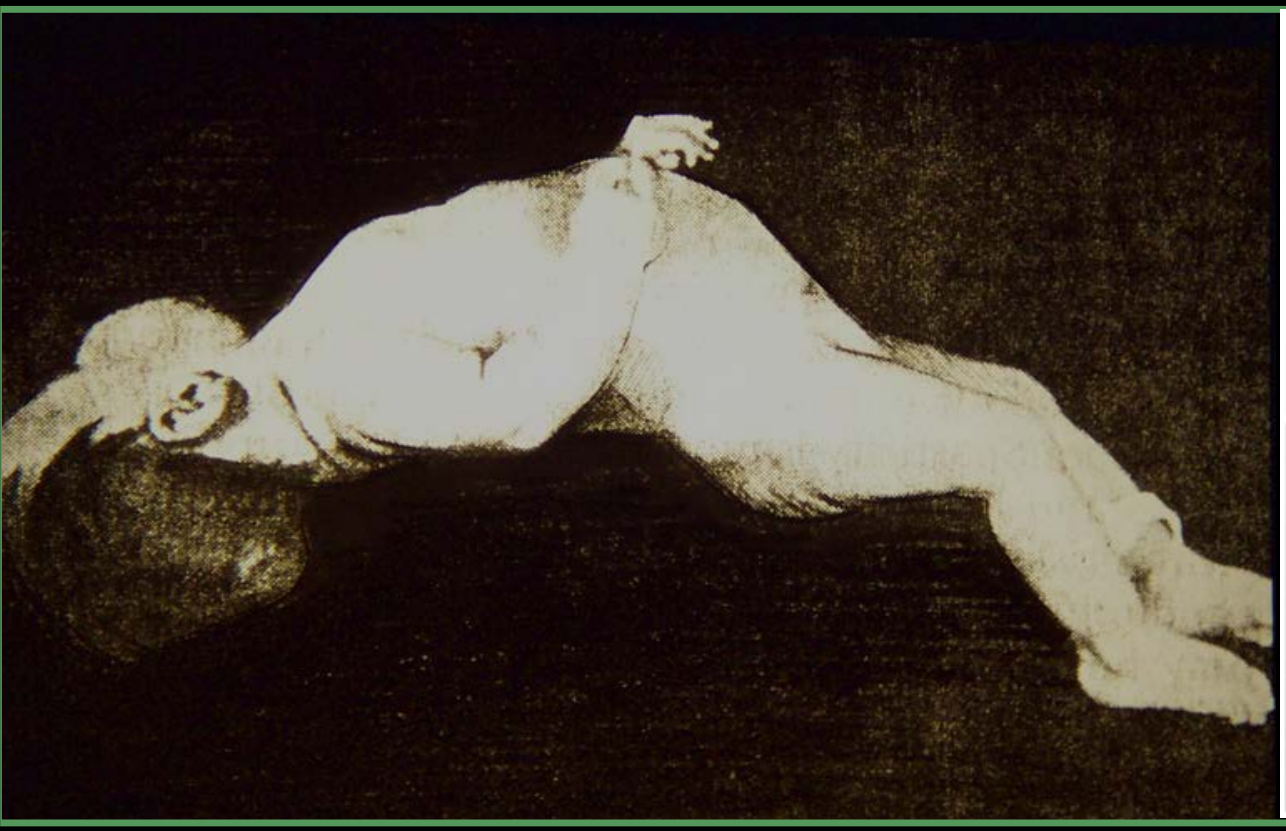


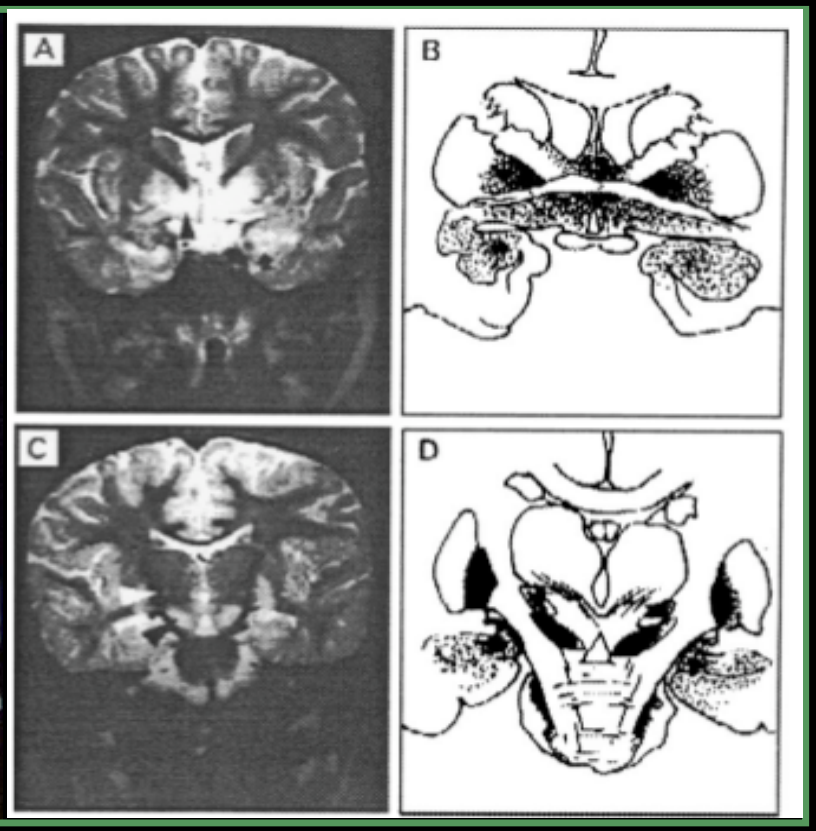
Figure 1. Plasma Branched-Chain Amino Acid and Glucose Levels in Patient 1, a Newborn Infant, during Treatment with Intravenous Branched-Chain Amino Acid–Free Amino Acids and Glucose or Oral Maple Syrup Urine Disease Formula (or Both) plus Insulin, Valine, and Isoleucine.

Diffuse basal ganglial, brain stem & cortical Edema in MSUD

The increased T2-signal in cortical & Deep gray matter is low-diffusion, intracellular Edema. In metabolic disorders like GA1 & propionic acidemia such Low-diffusion edema indicates irreversible cyto-toxic or ischemic injury of the Tissue.

The Gray-matter edema of MSUD is unique in its sensitivity to changes in serum osmolality: Increases in free water & progressive hyopnatremia cause worsening cyto-toxic edema & tissue death. Decreases in systemic free water Through The effects of furosemide & mannitol upon Kidney & brain, combined with the prevention of hypo-natremia by hypertonic saline are cyto-protective.





MRI from Morton DH et al Pediatrics 2002

CEREBRAL EDEMA IN AN 11 DAY OLD INFANT - CURRENT AGE 5 YEARS NORMAL DEVELOPMENTAL MILESTONES

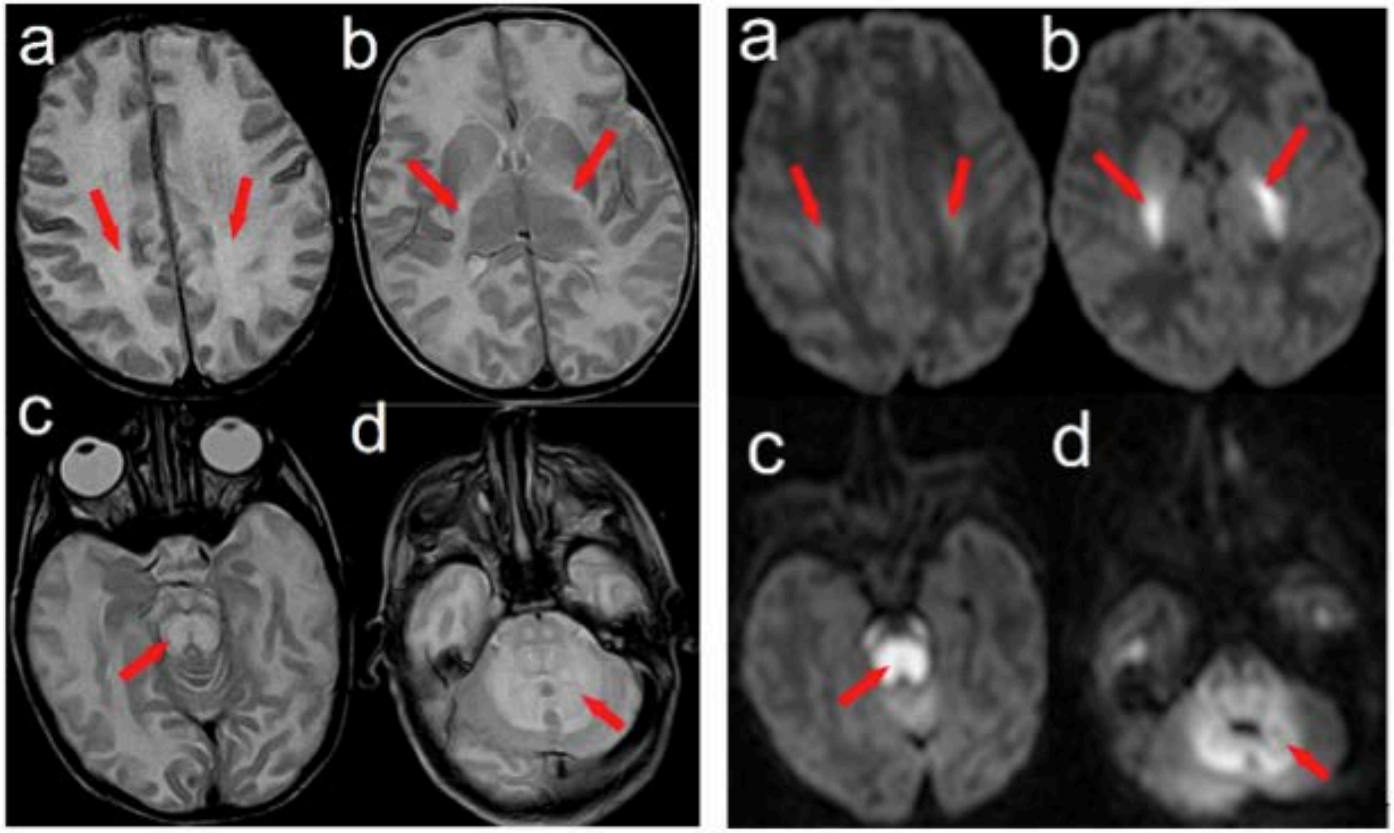
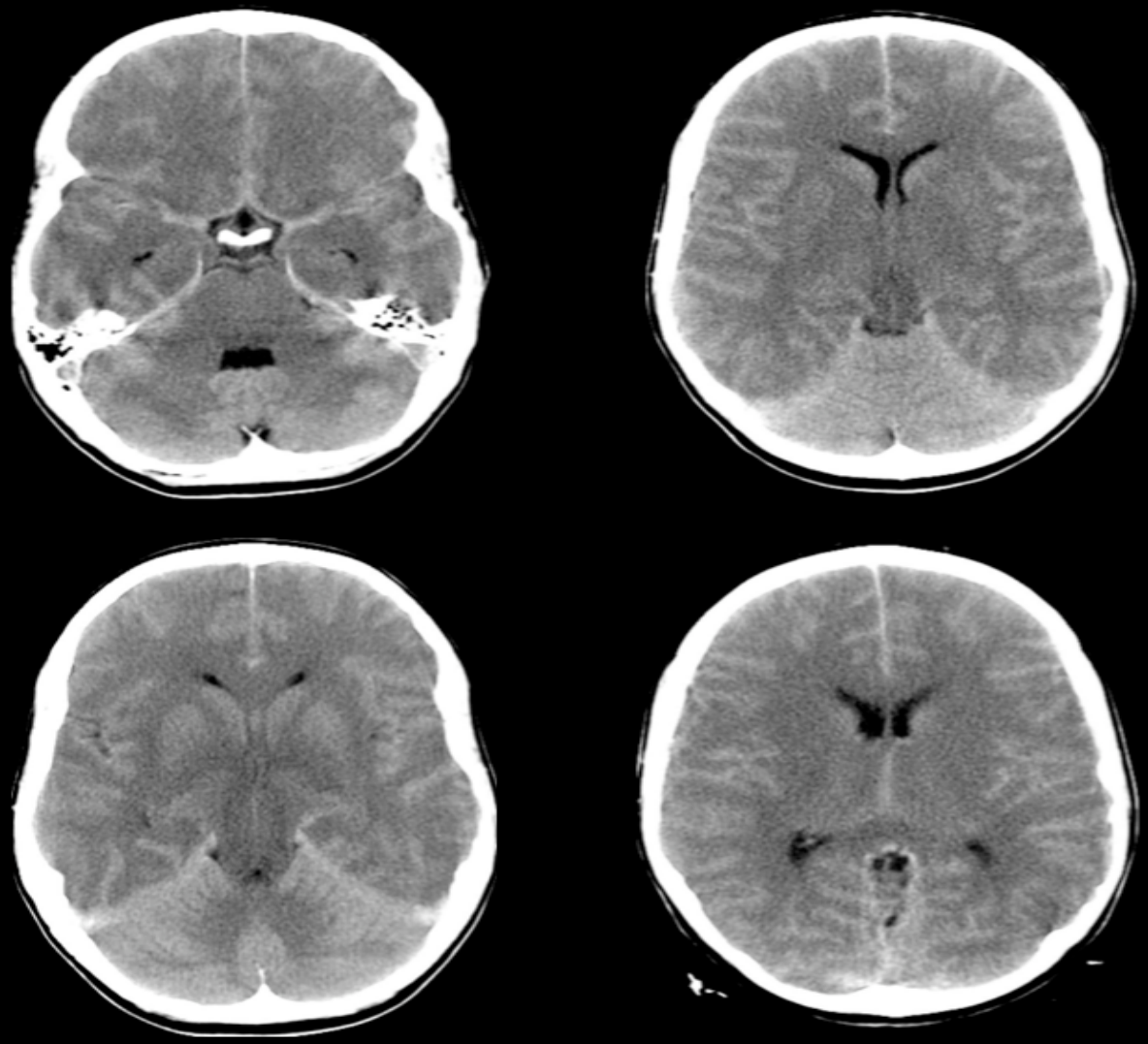


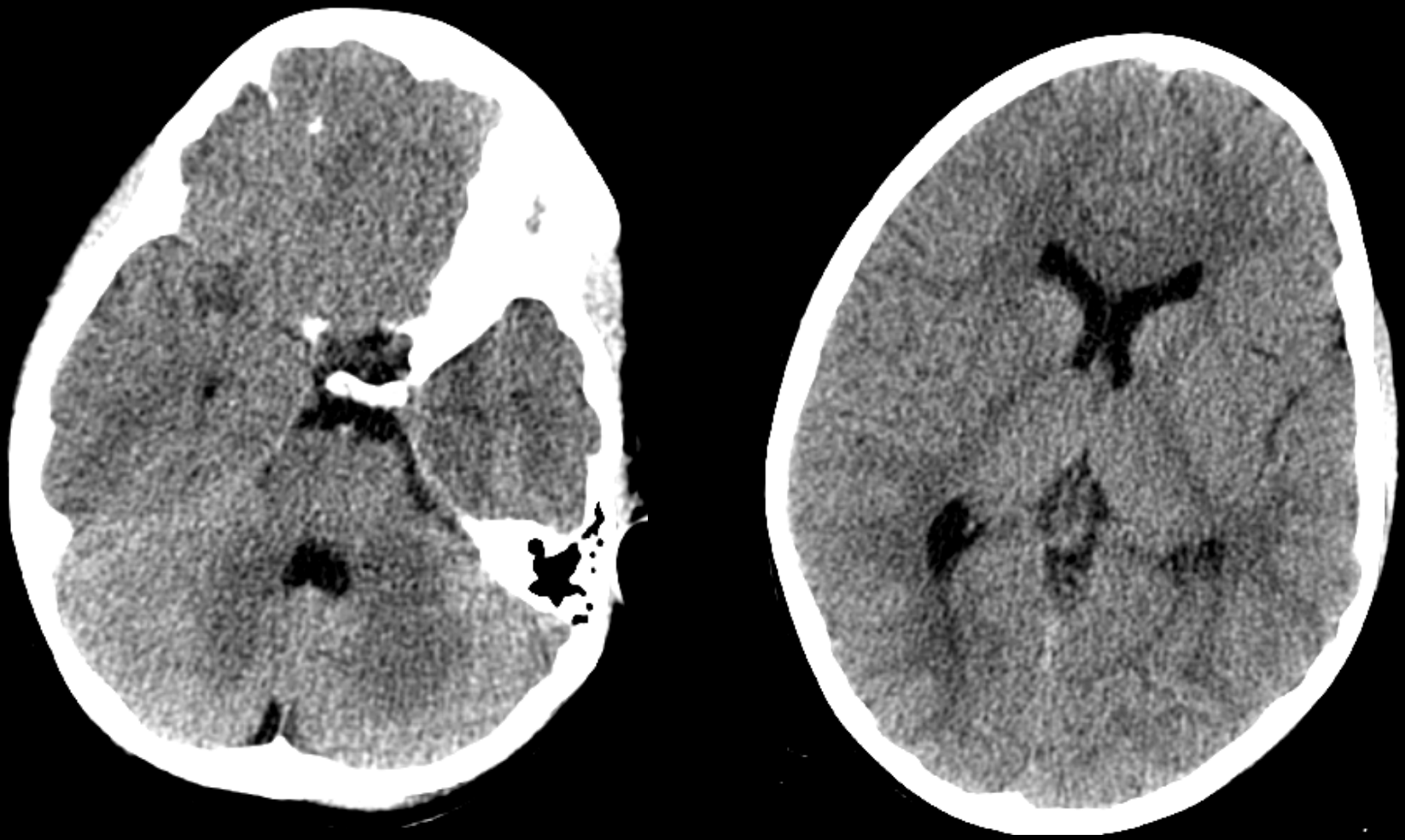
Figure **1-1**: Edema in an eleven-day old infant with Maple Syrup Urine Disease in acute metabolic crisis. **Left**: T2-weighted images: Generalized swelling is evidenced by overall hyperintensity in the brain as well as decreased subarachnoid and ventricular space. Focal areas of accentuated hyperintensity are present in the (a) posterior centrum semiovale (b) posterior limb of the internal capsule (c) midbrain and (d) cerebellum. **Right**: Diffusion-weighted images: increased intensity represents decreased diffusion. The images are overall hypointense, reflecting increased diffusion. Localized hyperintensities, reflecting restricted diffusion, are found in (a) the posterior centrum semiovale (b) the posterior limb of the internal capsule (c) the midbrain, and (d) the cerebellum. Image slices correspond with those on the left.

CT SCAN ON ADMISSION TO LGH



KZ was admitted to LGH 24 hours after being discharged from another hospital. He had a minor infectious illness but had become catabolic, was intoxicated with leucine, and had become encephalopathic. MSUD-parenteral nutrition was not available. The CT scan in the upper two panels was done *at the time of release* from the hospital and was read as "normal." The lower panel shows dangerous progression of the brain edema over a 24 hour period.

CT SCAN ON ADMISSION TO LGH



JoB was admitted to LGH 24 hours after onset of metabolic illness. He was intoxicated with leucine, and had become encephalopathis. The CT scan was done before the start of MSUD-TPN. The left panel shows CSF anterior to the brain stem, in the 4th ventricle, and posterior to the cerebellum. Also open ventricles & CSF in the left Sylvian fissure.

Prior to Discharge
48 hours after the brain CT

MSUD Admissions to Lancaster General Hospital for Acute Metabolic Care 1990-2012

Neonatal presentation acute illness	13%	35
Down syndrome *VSD repair, congenital bowel obstruction (HMC)*		
Sepsis SCID *(IL7-SCID)*		
Infectious illnesses	77%	203
Gastroenteritis (Rotavirus)		
Pneumonias (RSV)		
Otitis media		
Strep pharyngitis		
Bacterial/fungal sepsis		
Surgery & Trauma	10%	25
Appendicitis		
Cholecystitis		
Ovarian torsion		
Hysterectomy		
Fracture femur, skull fracture		

Overview of What Determines Outcome Beyond the Newborn Period for Patients with MSUD?

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Maple Syrup Urine Disease

21 years of "translational genetics"

+Presymptomatic diagnosis of high-risk newborns

+Parent education & home dietary management

+Metabolic monitoring and early detection of decompensation

+Improved MSUD-TPN to reverse metabolic intoxication

+Reversal of critical Brain edema & Prevention of strokes caused by cerebral edema

Elimination of Dialysis as an Invasive & Costly Treatment for Metabolic Crisis

+Recognition of brain under-nutrition as a major cause of mental and physical disability

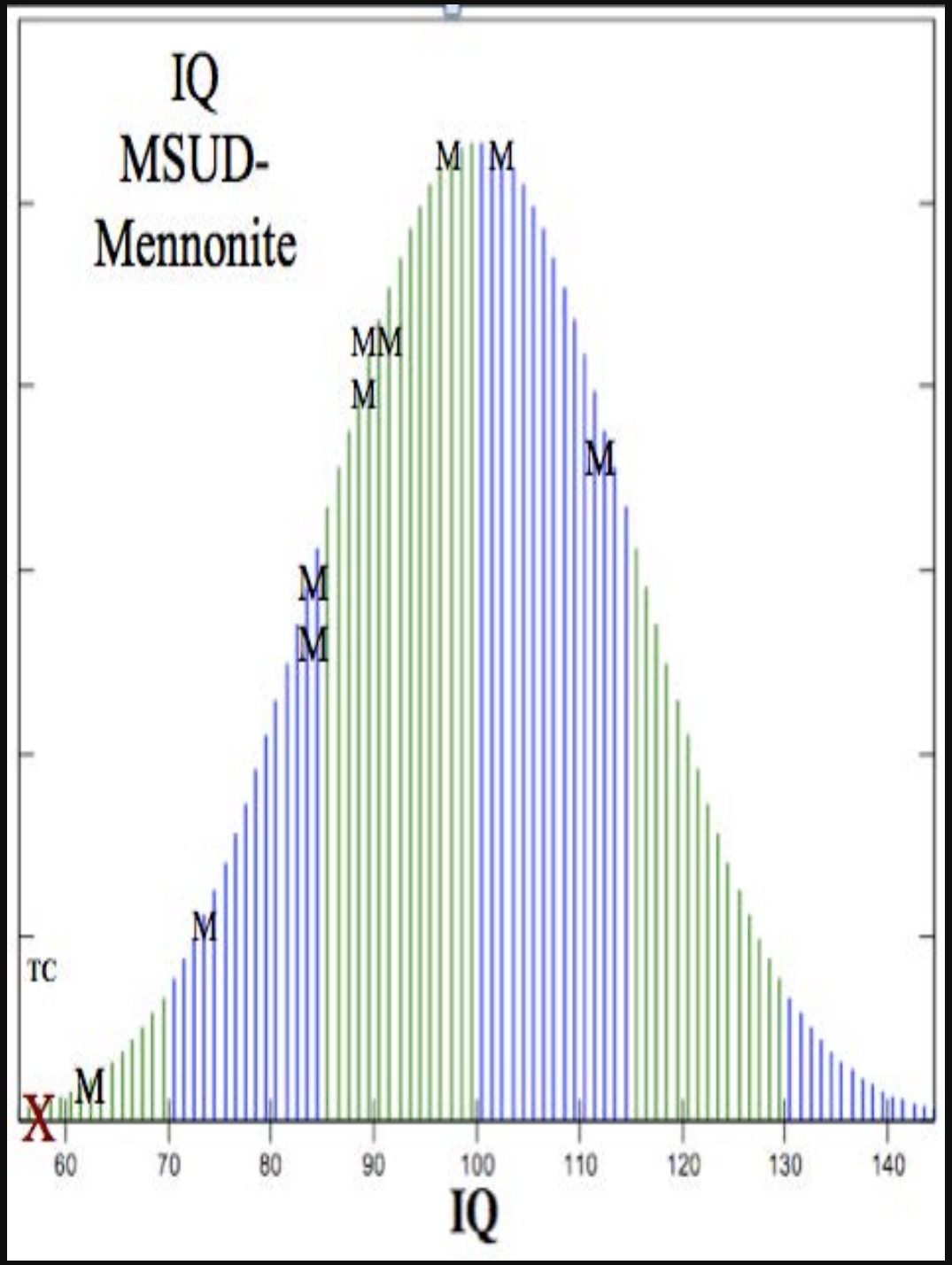
+Improved formula design for prevention of long-term dietary complications

+Recognition and treatment of mental illness in older children and adults

+Collaborative Development of a protocol for liver transplantation

+monitoring of patient outcomes with both conservative and transplant management

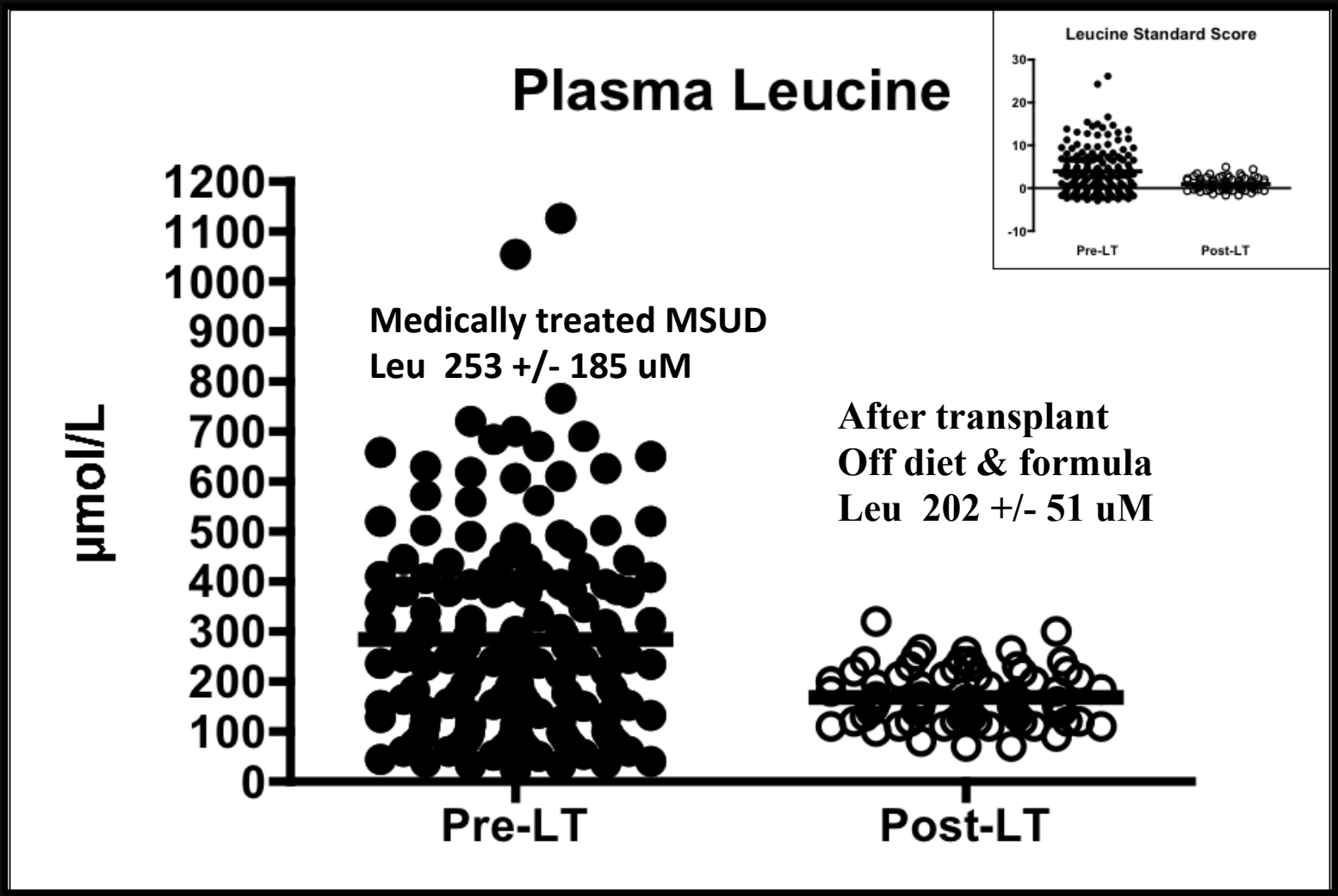
IQ CONTROL GROUP



2011

Liver Transplantation for Classical Maple Syrup Urine Disease: Long-Term Follow-Up in 37 Patients and Comparative United Network for Organ Sharing Experience

George V. Mazariegos, MD,* D. Holmes Morton, MD, Rakesh Sindhi, MD, Kyle Soltys, MD, Navdeep Nayyar, MD, Geoffrey Bond, MD, Diana Shellmer, PhD, Benjamin Shneider, MD, Jerry Vockley, MD, and Kevin A. Strauss, MD *



Post-Transplant – Plasma Amino acid Profiles on unrestricted diet not supplemented with LAT1 amino acids. The BCAA have high CNS uptake z-scores: Leu +2.6, Ile +4.1 & Val +2.8 while neuro-chemical precursors are low: Trp -1.2, Tyr 1.1, His -1, Met -1.1, & Thr -1.3. ARE POST-TRANSPLANT PSYCHOLOGICAL PROBLEMS RELATED?

		Amy Z	Mihir P	Kat Bur	Hahn	Louisa	Artur	Mean
		post trans	post trans	post trans				
		µmol/L						Z-SCORE
Leu	133(+/- 38)	175	271	322	278	250	120	2.6
Phe	52 (+/- 16)	46	87	65	54	67	43	-0.9
Trp	42 (+/-10)	31	68	52	33	40	30	-1.2
Lys	213 (+/- 46)	75	188	159	174	182	49	-0.3
Arg	90 (+/- 32)	68	43	118	148	63	56	0.4
Tyr	67 (+/- 18)	32	66	69	53	84	44	-1.1
Orn	64 (+/- 23)	28	122	71	78	130	34	-0.3
Ile	81 (+/- 29)	134	184	239	217	200	95	4.1
His	99 (+/- 20)	48	118	76	92	68	74	-1.0
Val	275 (+/- 57)	333	468	519	536	383	309	2.8
Gln	590 (98 +/- 98)	458	280	565	631	530	518	-0.7
Met	29 (+/- 8)	14	38	28	28	28	23	-1.1
Thr	142 (+/- 48)	46	100	110	122	97	107	-1.3
	Sum AA	1488	2033	2393	2444	2122	1502	

Influx

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Among the 7 patients with Adaptive & IQ Scores <70 were patients from South America & India where MSUD formula, Ile/Val supplements, blood amino acid monitoring, & sick day treatment protocols are not available. In Vietnam where screening for MSUD was recently introduced medical services are not available – 11 of 12 infants diagnosed over 3 yrs of the program are dead. The 1 survivor is disabled. Unfortunately, several of these transplanted patients were from regions of the United States where medical care is inadequate & outcomes are poor even for infants diagnosed through newborn screening.

Regardless of their disabilities, medical reasoning suggested to us that cure of MSUD by liver transplant was likely to stabilize the medical condition, there-by decreasing the risk of further injury. Ethical reasoning suggested cure of MSUD would improve the quality of life for patient & family.

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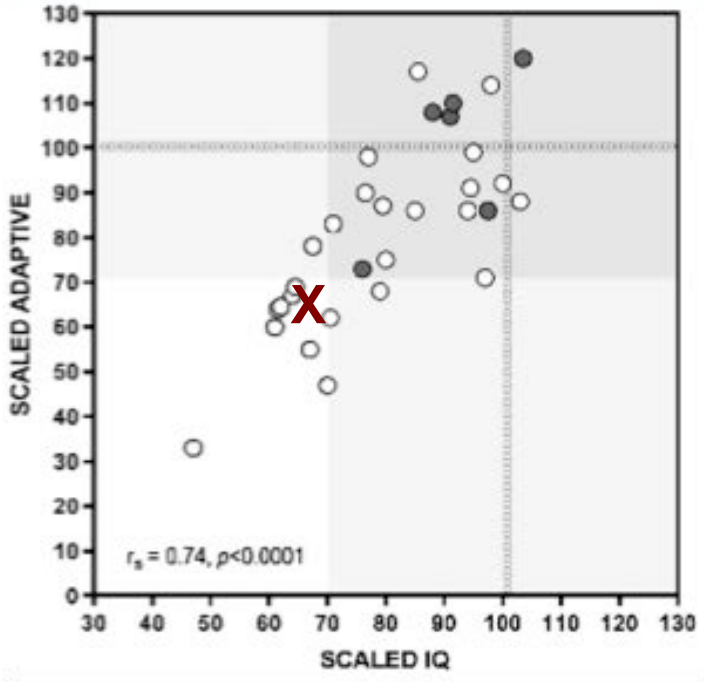

Figure 2. In 33 pretransplantation patients, there was a strong correlation between IQ (*x*-axis) and adaptive function (*y*-axis). Only 3 patients had IQ scores at or above the mean (100; *dotted line*). One-third had IQ scores in the deficient range (≤70). *Shaded areas* represent the mean ± 2 SD in normal subjects. *Gray circles* represent Old Order Mennonite subjects and indicate that different cultural background did not bias toward lower test scores. *Open circles* indicate non-Old Order Mennonite patients.

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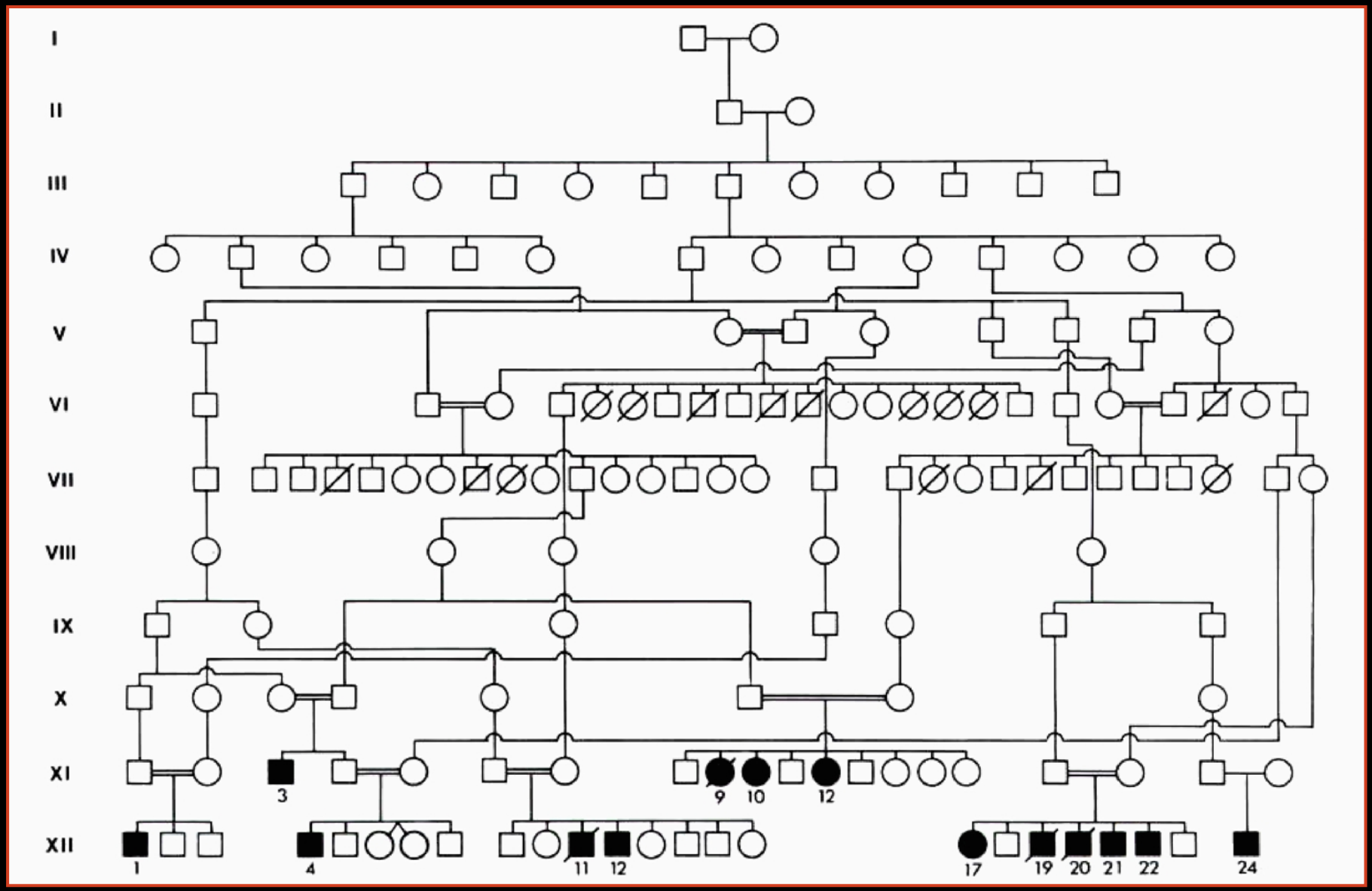
Amish Cerebral Palsy, ca. *1989*



Mitochondria

Lysine

Hydroxylysine

Tryptophan

Glutaric acid?

Glutaryl-CoA Synthetase?

Glutaryl-CoA → Glutaric acid

Glutaryl-CoA dehydrogenase

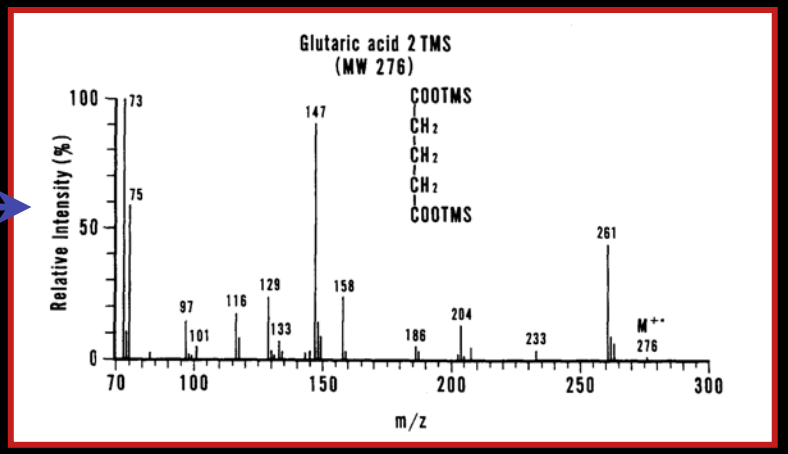
FAD

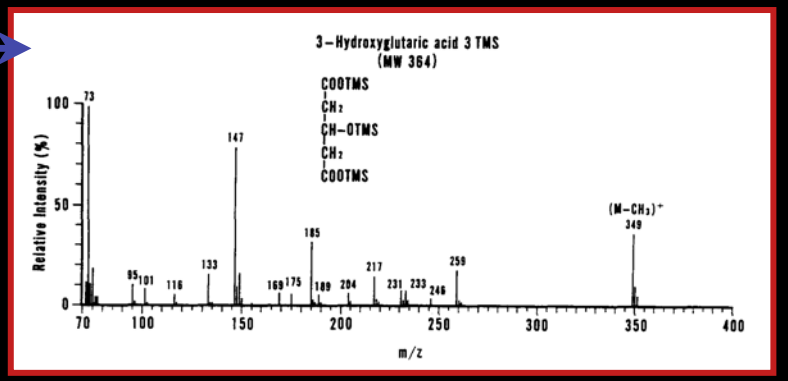
FAD·2H

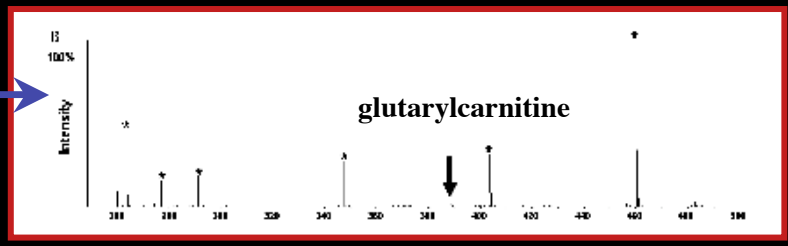
Glutaconyl-CoA

Acetyl-CoA

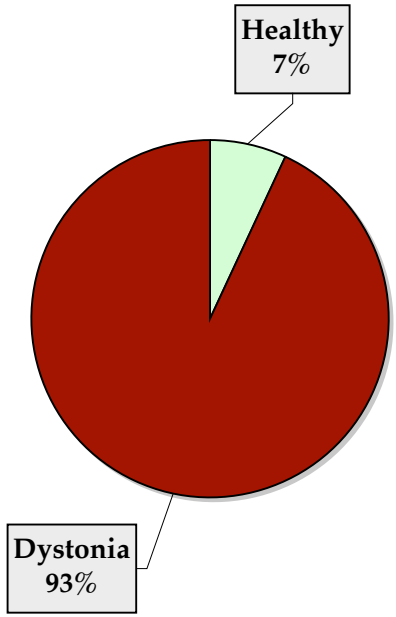
Tissues (brain), blood, urine







Not Screened (N=171)



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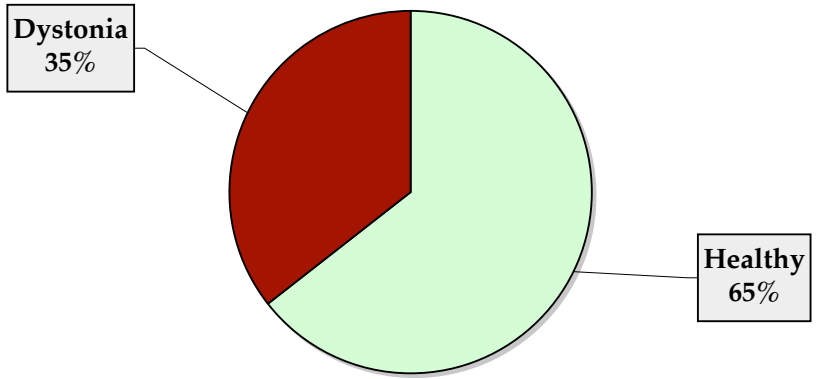


Dystonia

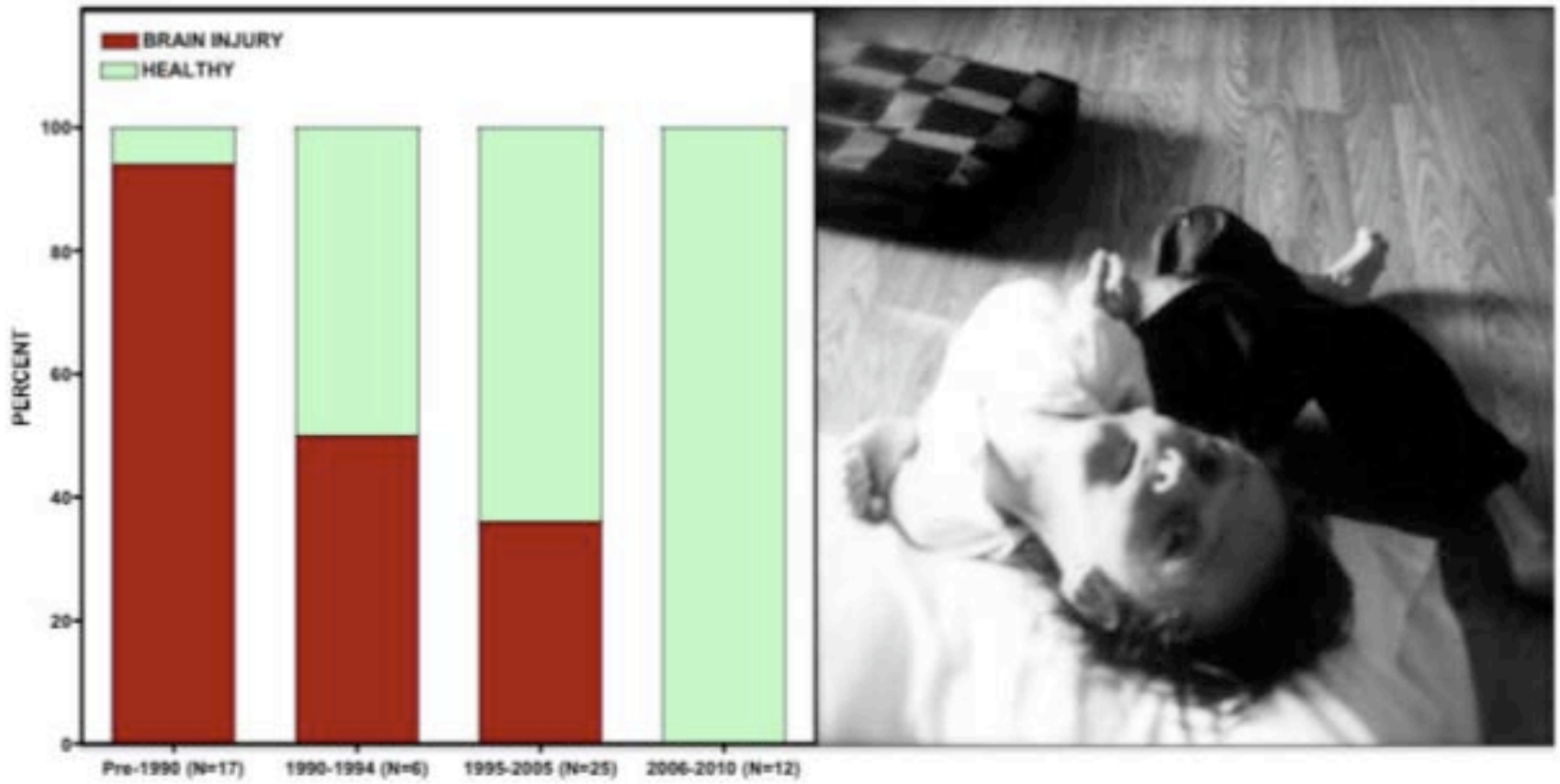
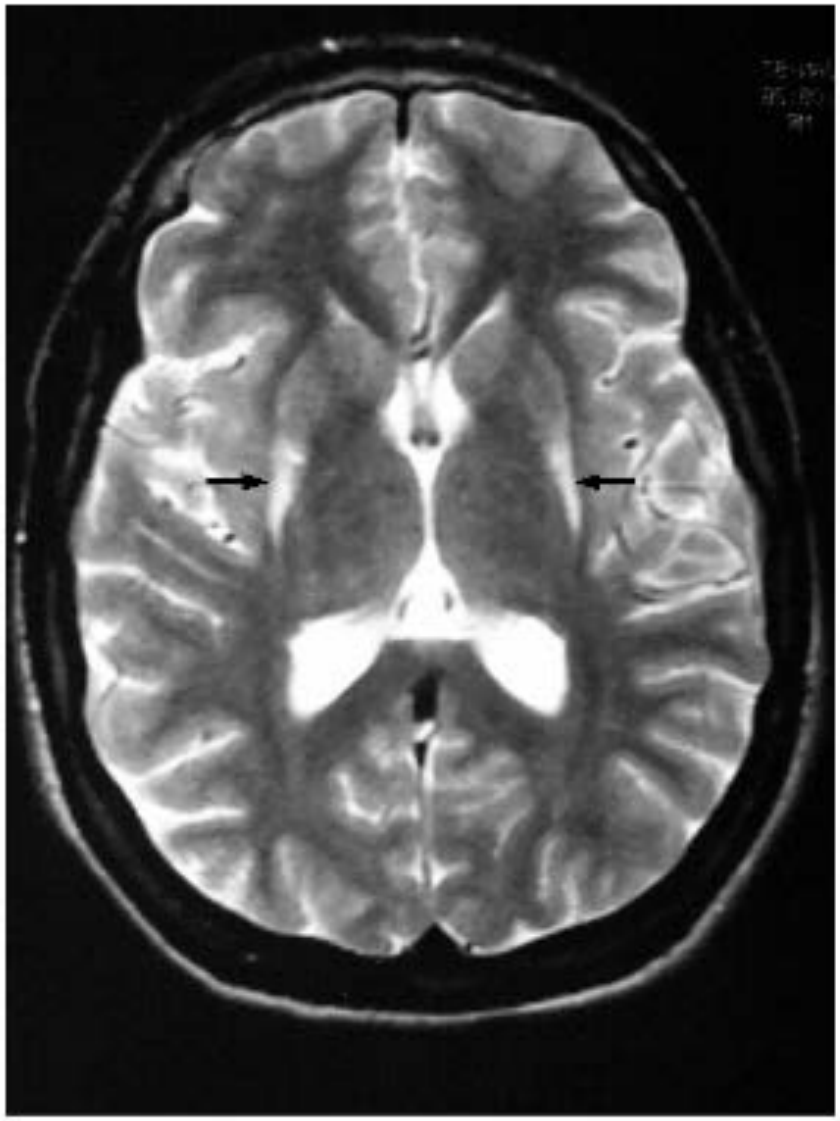


Figure 1. Before 1989, Amish children with glutaryl-CoA dehydrogenase deficiency (GA1) were fully disabled by their second birthday and often misdiagnosed with cerebral palsy. The first genetic study at the Clinic for Special Children identified GA1 as the cause of "Amish cerebral palsy" in 16 children. Beginning in 1989, the Clinic offered on-site diagnostic screening, comprehensive pediatric follow-up care, and inpatient management for children with GA1. The incidence of brain injury decreased from 94% to 36% by 1990. There have been no brain injuries among our 12 GA1 patients born after 2006.

Crippling dystonia follows acute striatal necrosis in an Amish child with GA1



Transport Competition

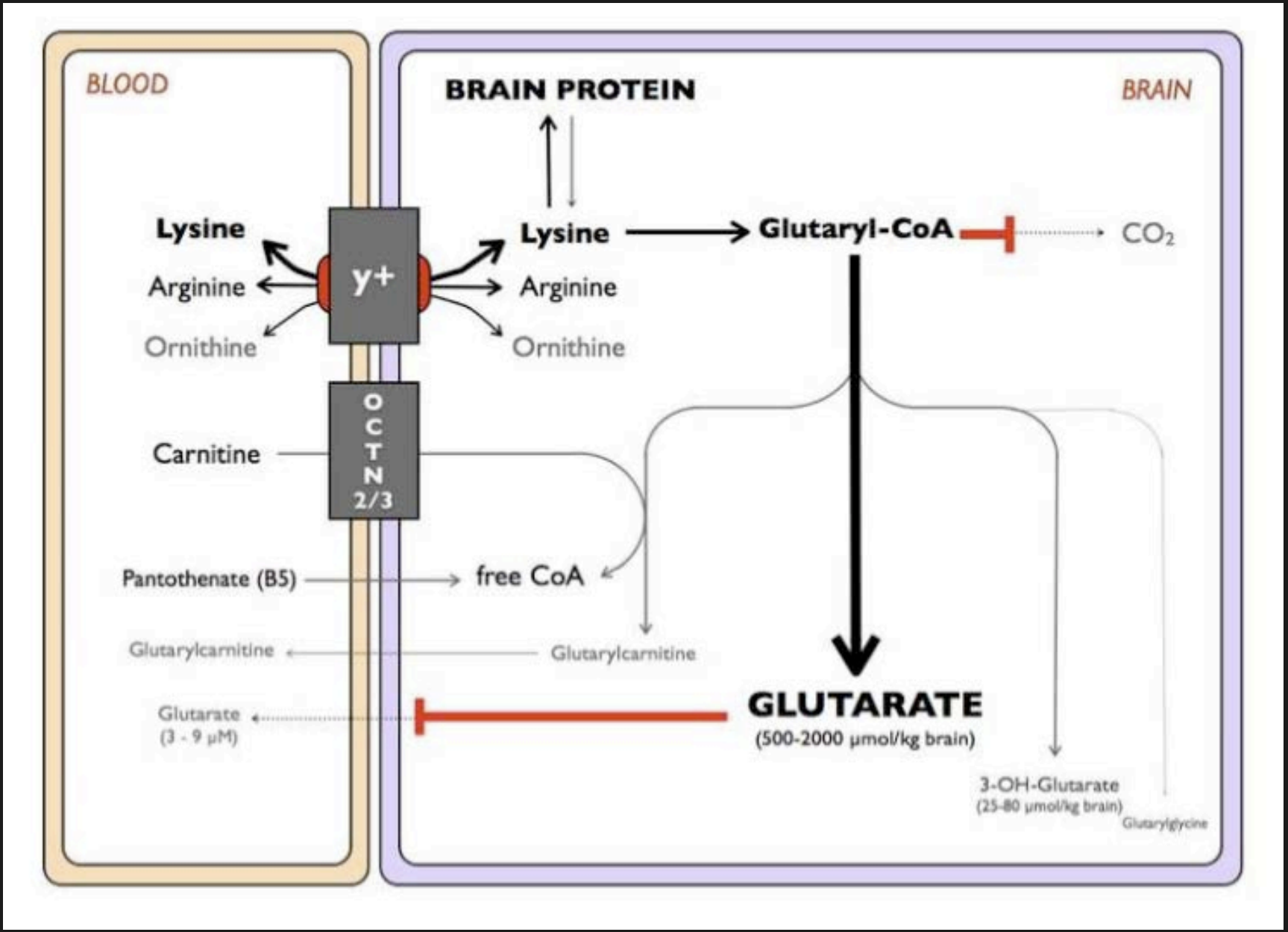
Effects free amino acids upon the plasma Lysine/Arginine Ratio

Pathophysiology and treatment of glutaryl-CoA dehydrogenase deficiency: Lysine restriction coupled to arginine fortification improves neurological outcome.

Accepted for publication June 30, 2011 by *Molecular Genetics & Metabolism*, exactly 23 years after my first visit to Lancaster County to examine Danny Lapp, the first Amish infant diagnosed with glutaric aciduria type 1.

Transport Competition

Nutritional effects on the developing brain



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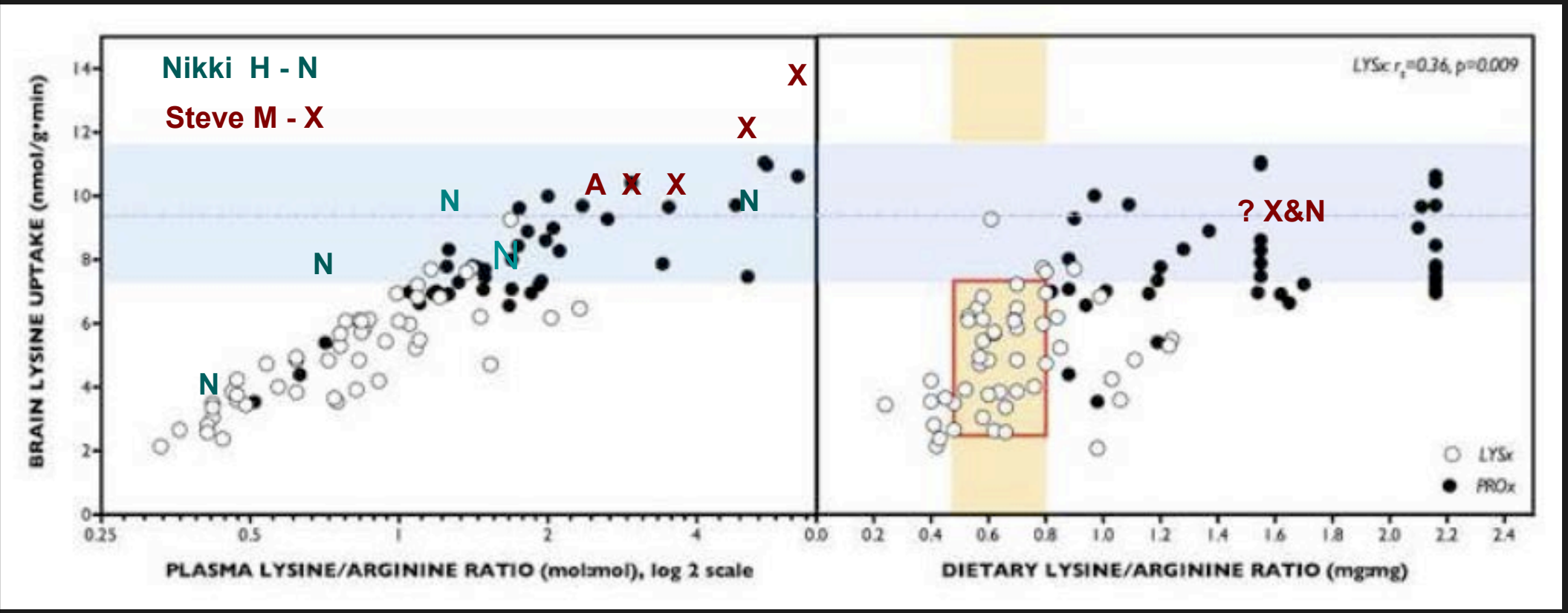
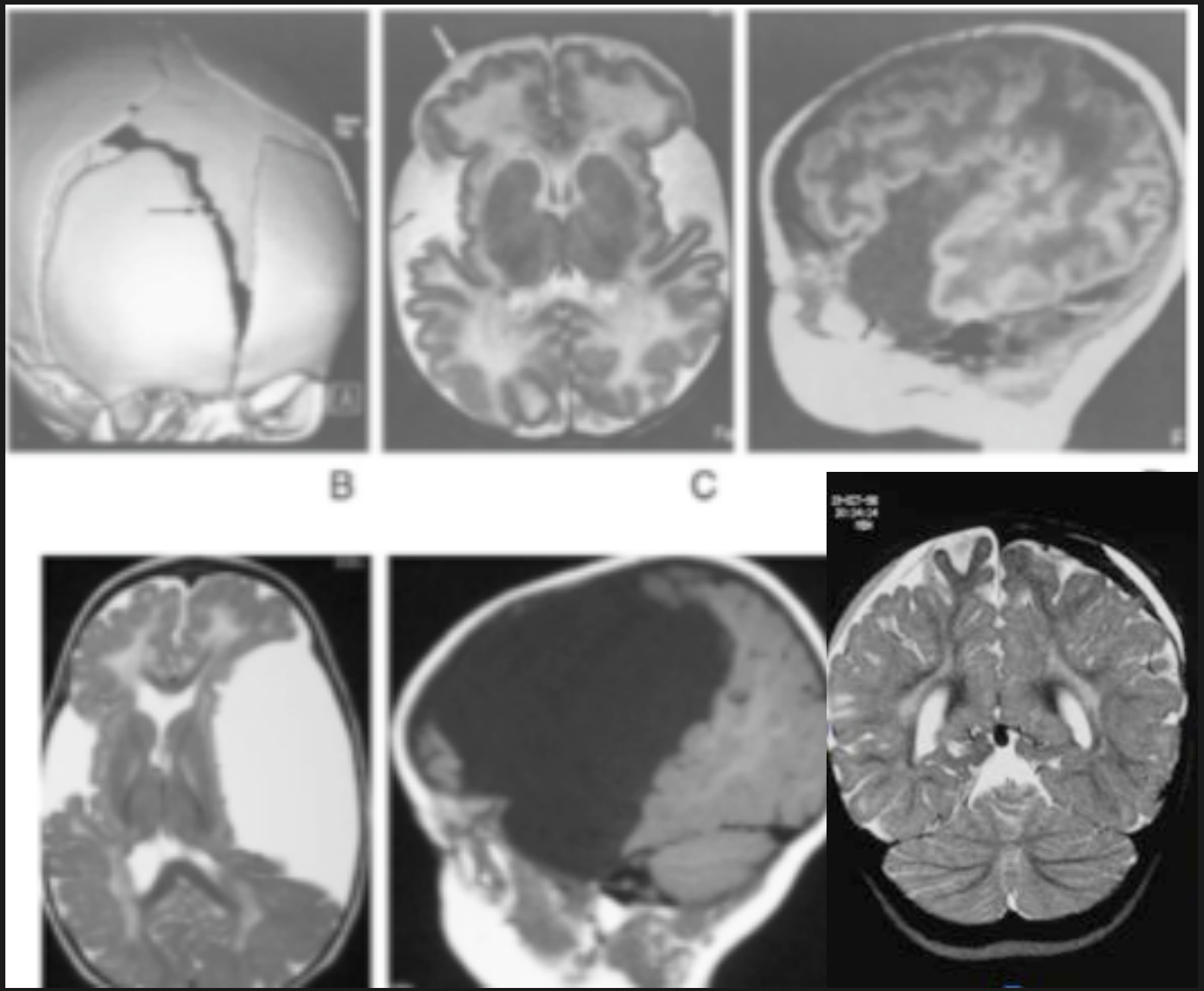
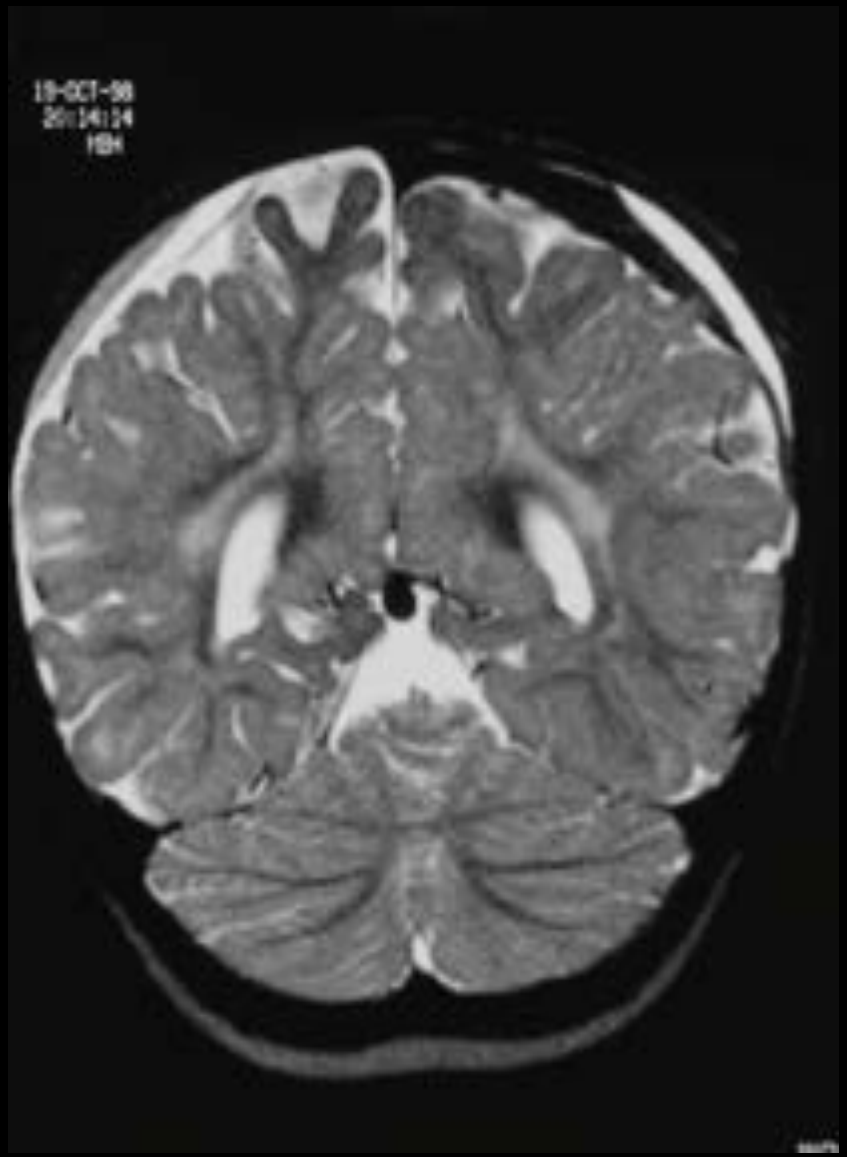


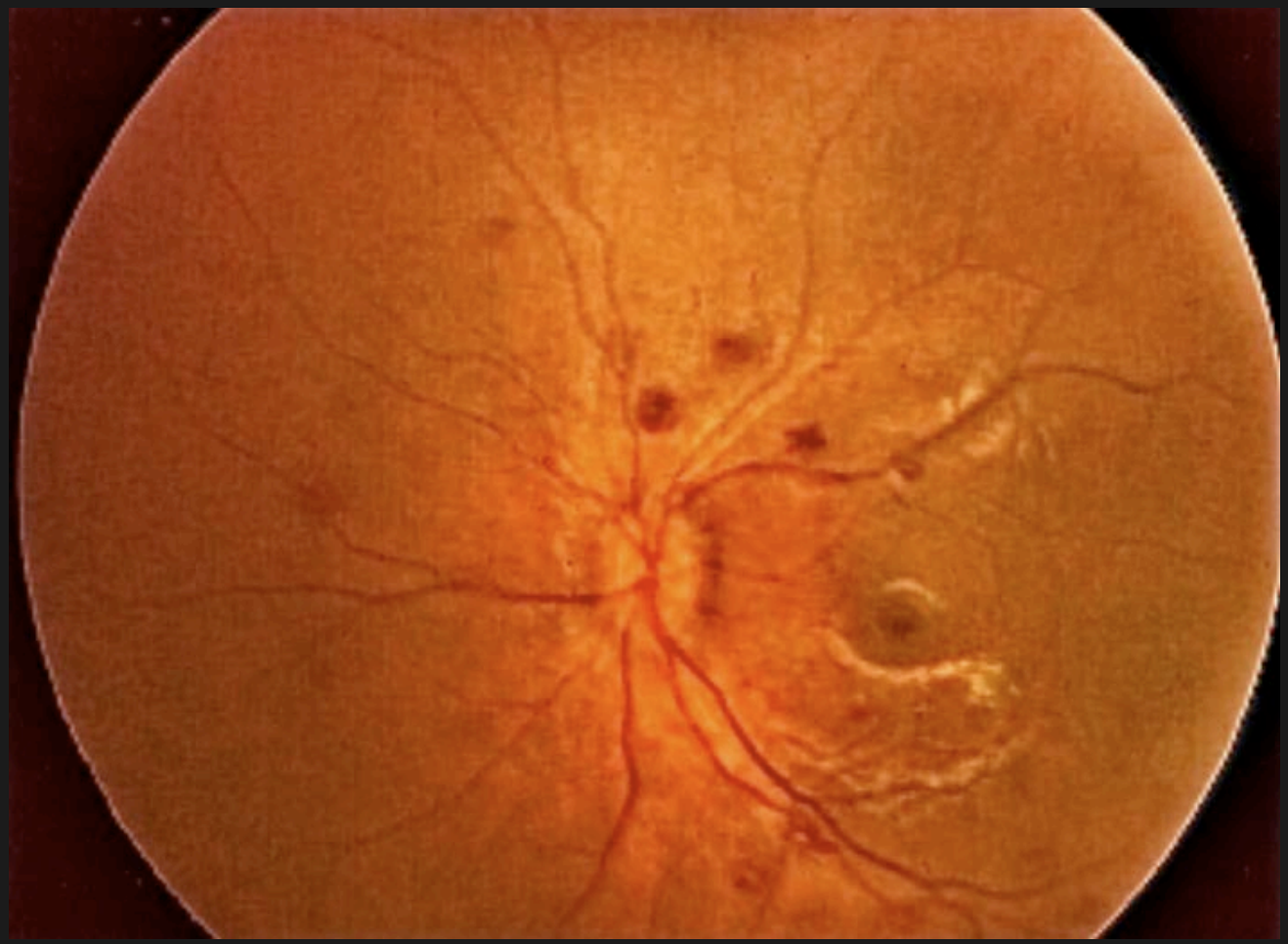
Injury or Disease?



GA1: Intracranial Hemorrhage



Retinal hemorrhage
Glutaric Aciduria Type 1



Nikki GA1, non-Amish, diagnosed by screening

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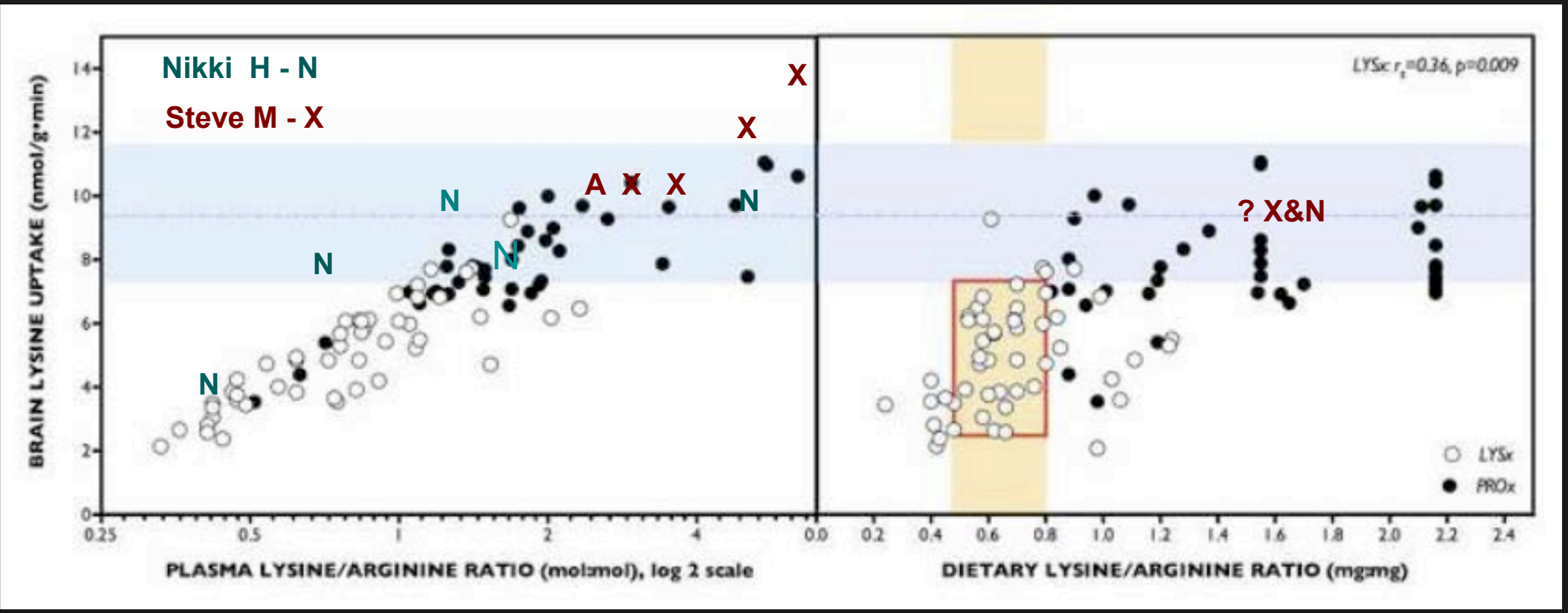

Genomics & A Medical Home

A Medical Home is the place where,
when you have to go there,
they have to take you in,
And, they know how to care for you.

D. Holmes Morton MD
Pediatrician, Clinic for Special Children
Strasburg, Pennsylvania