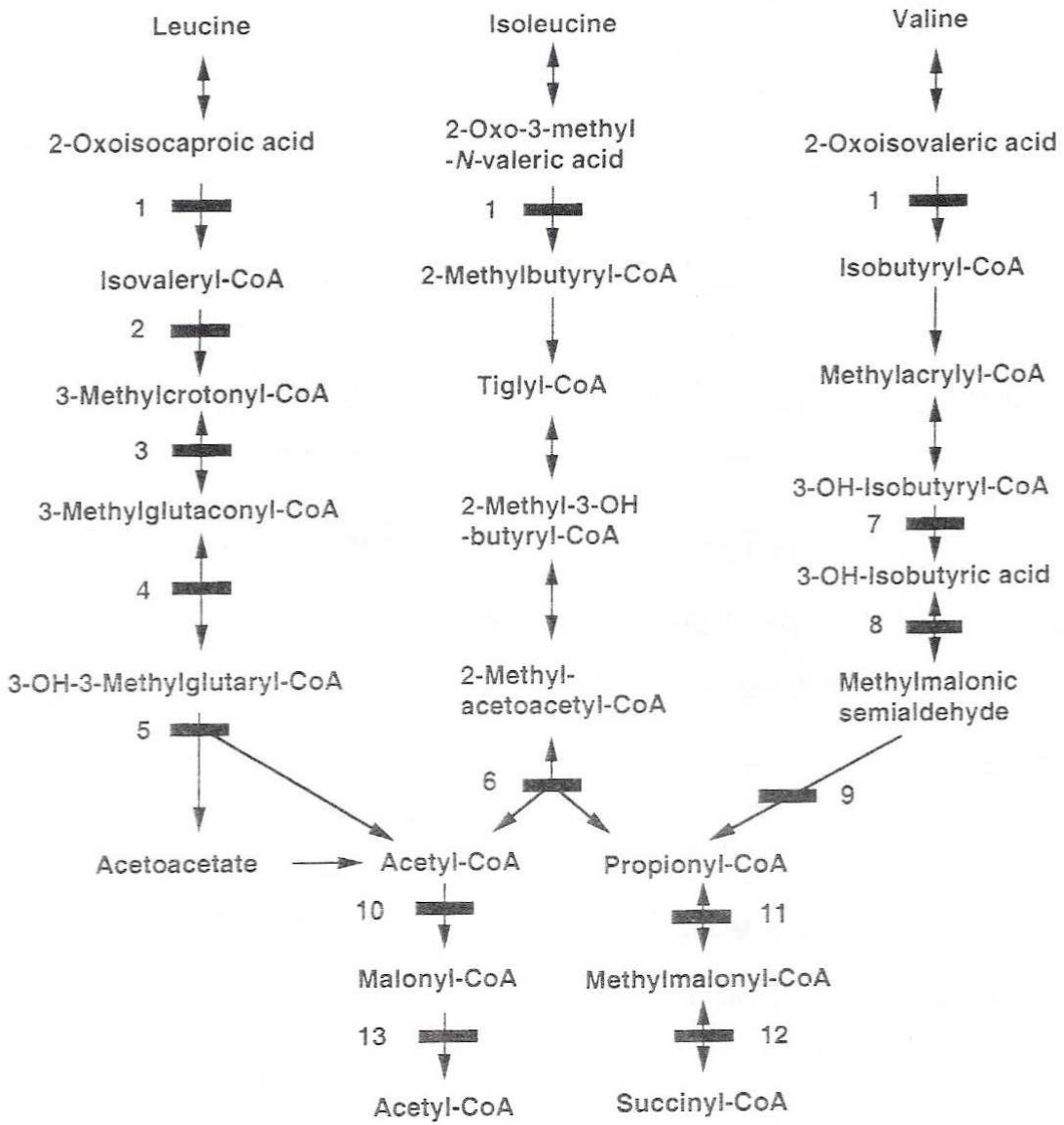
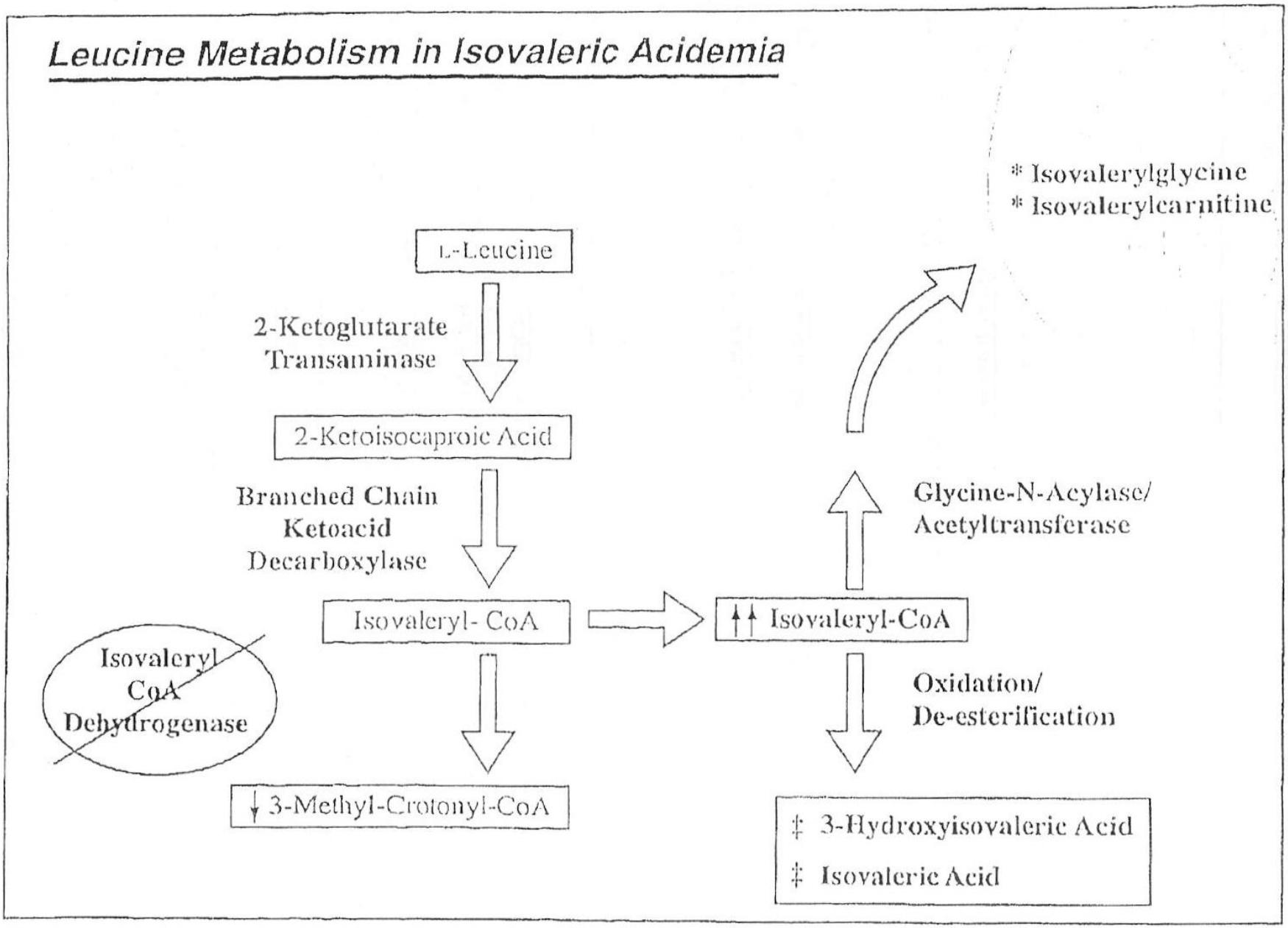
Isovaleric aciduria

2008



16.1. Pathways of branched-chain amino acid catabolism. 1, Branched-chain oxo- (or keto-) acid dehydrogenase; 2, valeryl-coenzyme A (CoA) dehydrogenase; 3, 3-methylcrotonyl-CoA carboxylase; 4, 3-methylglutaconyl-CoA hydratase; 5, ydroxy-3-methylglutaryl-CoA lyase; 6, 2-methylacetoacetyl-CoA thiolase; 7, 3-hydroxybutyryl-CoA deacylase; 8, 3-droxyisobutyric-acid dehydrogenase; 9, methylmalonylsemialdehyde dehydrogenase; 10, acetyl-CoA carboxylase (in osol), propionyl-CoA carboxylase (in mitochondria); 11, propionyl-CoA carboxylase; 12, methylmalonyl-CoA mutase; 13, lonyl-CoA decarboxylase. Enzyme defects are indicated by *solid bars*



* *Toxic metabolites*

‡ Nontoxic and excreted in the urine

Birth and perinatal history

- 38+3 weeks. First born. Birth weight 3.35kg. Normal vaginal delivery in Kwong Wah Hospital. Discharged on Day 3.
- Non-consanguineous marriage

- On mixed feed, but poor feeding, baby was drowsy all along, took 1 hour to finish one feed, no cyanosis.

Signs and symptoms

Presentation

- Day 9
- Lethargy
- Respiratory distress with pneumonia
- Smelly feet

Treament

- Intubated
- Sepsis work-up
- Start of antibiotics

Initial investigations

- CRP 300 (7th Jan)→69→33 (on 17th Jan)
- WBC : 3.2 → 1.1x 10^9 /Litre;
  Neutrophil: 1.1 → 0.1
  HB : 16.8 → 12.1 g/dl
  Platelet :101 → 10 x 10^9 / Litre
- Hypocalcaemia: Total calciium 1.11 mmol/L
- Persistent metabolic acidosis pH 7.2. Base excess -11 mmol/L. Anion gap up to 20. Ammonia 214 mmol/L. Glucose 8-9 mmol/L.

Differential diagnosis and then diagnosis

- Clinical: Isovaleric aciduria
- Chemical diagnosis on day 3 - Urine:
  ↑ isovalerylglycine, 3- and 4-hydroxyisovaleric acid, methylsuccinic acid
- Genetic diagnosis on day 10:

  Father: heterozygous for p.Y371C;

  Mother: heterozygous for c.1148_1151dupGCTA(p.Y355X)

  Patient icompound heterozygous for the above two mutations,

Treatment

- Decrease protein supply and prevent catabolism – parenteral nutrition, to low leucine diet
- Toxin removal:

  Exchange transfusion double volume done 4 times in 24 hours; Planned hemofiltration but then withheld
- Alternate pathways:

  Arginine, Glycine

Collaboration with other hospitals

- Via email to members of HKSIEM, ask for glycine and experience
- Dozens of response – negative
- Dr Joanie Hui called up the Royal Children Hospital, Melbourne for glycine
- Glycine got on board the plane departing at night
- In the early morning, glycine at the Customs
- Joanie and I went to the Customs at the airport
- We declare to the customs as “health food”

Some row on dispensing, prescribing, weighing, packing, and delivering an ‘illegal drugs’

Table. Chronologic data, pertinent clinical information, and ef

Patient	Age (yr), sex, clinical phenotype	Age at onset*; treatment†	Developmental outcome
A	10 1/12, M, acute	Day 3; day 8	IQ 82 (low avg), WISC-R (7 1/12 yr¶)
B	10 1/12, F, acute	Day 13; day 16	IQ 70 (borderline/mild MR), WISC-R (8 6/12 yr)
C(1)	5 1/12, M, acute	Day 3; day 7	IQ 49 (moderate/mild MR), Stanford-Binet (3 1/12 yr)
C(2)	1 11/12, M, acute	Day 3; day 4	DQ 103, Gesell (7/12 yr)
D	1 1/12, M, acute	Day 1; day 16	DQ 115 (MDI), 99 (PDI), Bayley** indices for cognitive (MDI) and motor (PDI) development (1 1/12 yr)
E	14 1/12, F, chronic	2 1/12 yr; 3 1/12 yr	IQ 68 (borderline/mild MR); WISC-R (12 1/12 yr)
F	9 1/12, F chronic	Day 15; 3 10/12 yr	IQ 67, Stanford-Binet (5 yr); IQ 62 (mild MR), General Cognitive Index (8 yr)
G	9 1/12, M, chronic	3/12 yr; 1 11/12 yr	DQ 58, Gesell (1 11/12 yr); IQ 79 (borderline/mild MR), WISC-R (7 10/12 yr)
H	7 10/12, F, chronic	—; 4/12 yr	IQ 97, WPPSI (6 5/12 yr)