



Clinical Experience and Applicable Guidelines for the Management of Homocystinuria

Betaine anhydrous across the homocystinuria

CBS deficiency • severe MTHFR deficiency • cobalamin-related remethylation disorders

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شما در امروز هستیم. مشتاقانه منتظر همکاری با

International lecture | 45minutes

S. Matsumoto

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COI Disclosure

Shiro Matsumoto

Kumamoto University

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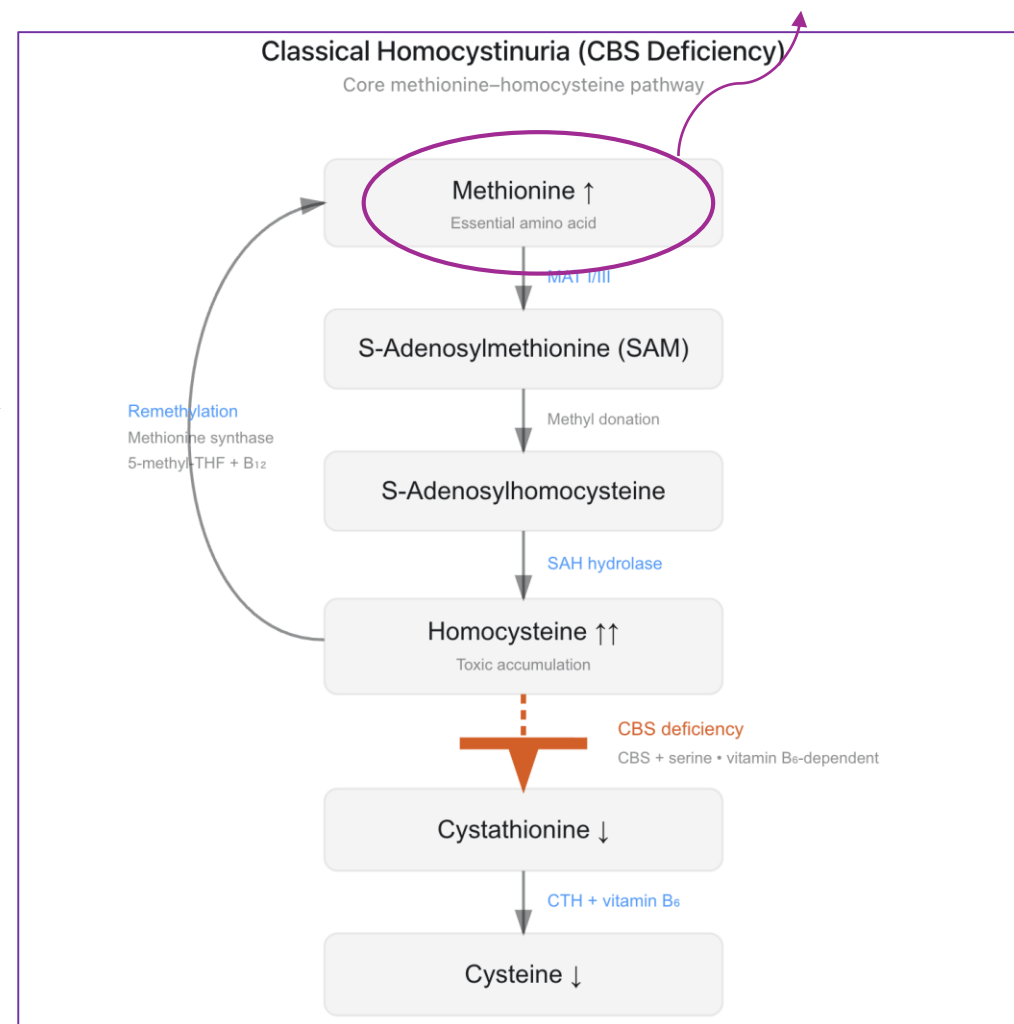
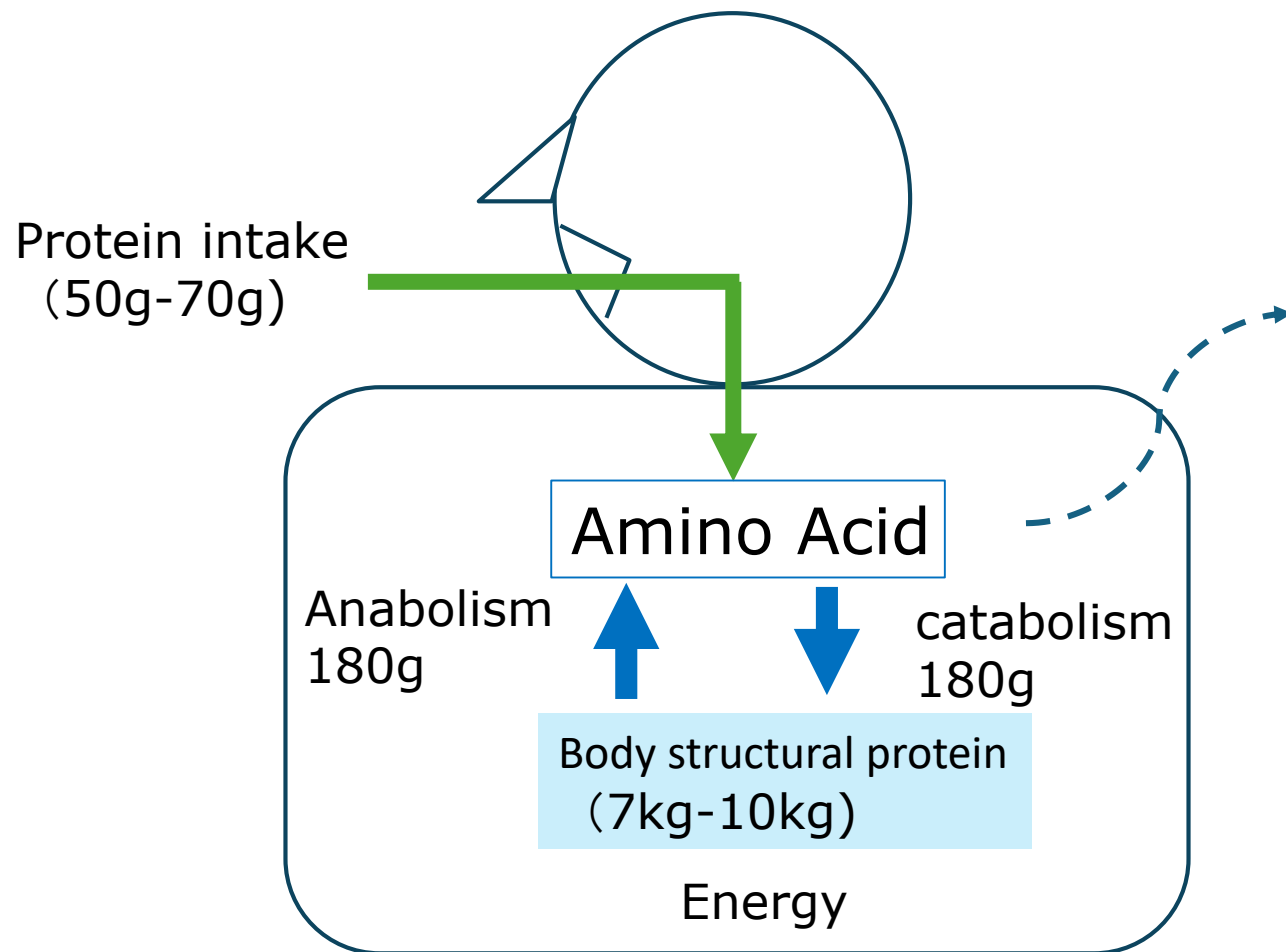
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Outline

- Overview : What is Homocystinuria
هموسیستینوری چیست؟
- Clinical feature : our cases and experiences
پرونده‌ها و تجربیات ما
- Management with **CYSTADANE® | BETAINE ANHYDROUS** based on Guidelines
مدیریت مبتنی بر
دستورالعمل‌ها

Overview : What is Homocystinuria

New born screening by Dried Red Spot

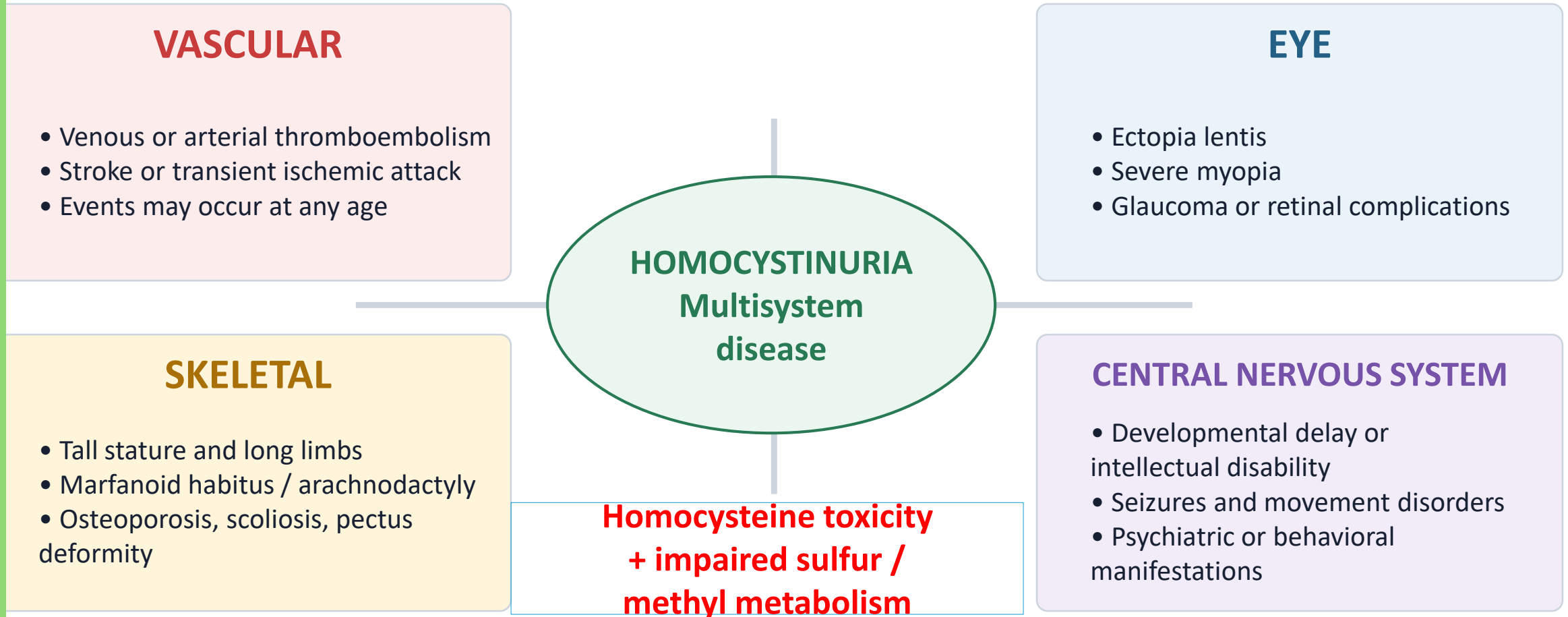


هوموسیستینوری ناشی از اختلال در آنزیمی است که برای متابولیسم اسید آمینه متیونین لازم است، که منجر به تجمع مقادیر زیادی هوموسیستین در بدن می شود و در نتیجه باعث بروز علائم می گردد.

(Matsumoto et al, Acute decompensation in Metabolic disease, Japanese Journal of Pediatric 2019)

Clinical Manifestations of Homocystinuria

Four major systems in classical CBS deficiency



Phenotype varies by biochemical subtype, age at diagnosis and treatment. Remethylation disorders often present predominantly with neurologic and multisystem disease.

Points to note

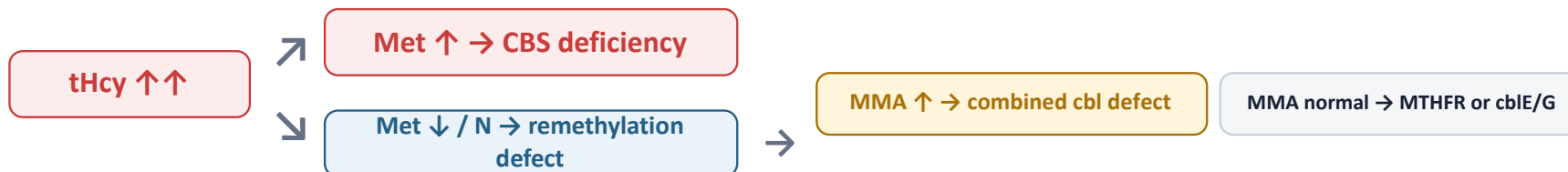
3 of 4 subtypes are Not detected by NBS
 درادن دوجو یرگلابرغ ناکما، یرامیب عونریز راهچ زا دروم هس یارب

Biochemical Fingerprints of Inherited Homocystinurias

Methionine is the first major branch point

	METHIONINE ↑	METHIONINE ↓ OR NORMAL — REMETHYLATION DISORDERS		
Biomarker	CBS deficiency	MTHFR deficiency	cblE / cblG	cblC / cblD-combined cblF / cblJ
Plasma tHcy	↑↑	↑↑	↑↑	↑↑
Plasma methionine	↑	↓	↓ / N	↓ / N
Methylmalonic acid	Normal	Normal	Normal	↑↑
Plasma cystathionine	↓	N / ↑	N / ↑	↑
Plasma / CSF 5-MTHF	Normal	↓	Variable	Variable
Most discriminating clue	High Met + low cystathionine	Low 5-MTHF + normal MMA	Normal MMA + MTR/MTRR defect	MMA ↑ + tHcy ↑

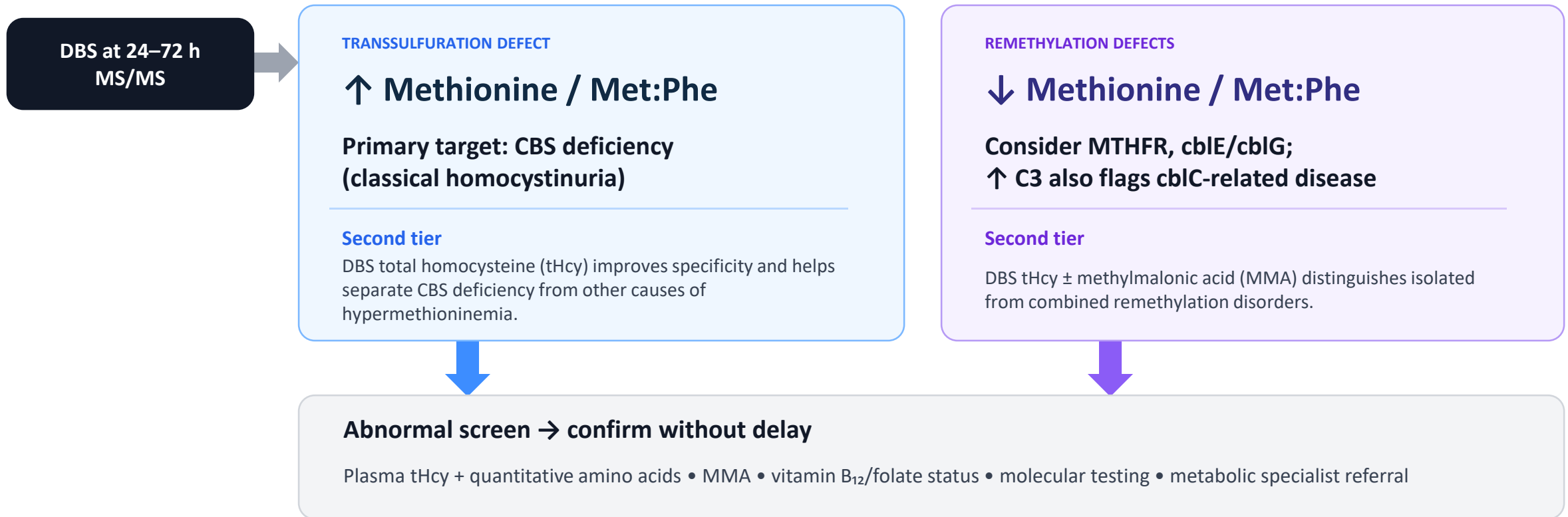
Rapid biochemical
triage:



N = normal. Interpret pretreatment samples; confirm with targeted metabolites and molecular testing.

One analyte cannot detect every homocystinuria

Interpret the dried-blood-spot pattern according to the disrupted pathway



A normal screen does not exclude disease

Methionine-based NBS can miss early-sampled or pyridoxine-responsive CBS deficiency—and remethylation disorders if low Met is not flagged. If clinically suspected, measure plasma tHcy regardless of NBS.

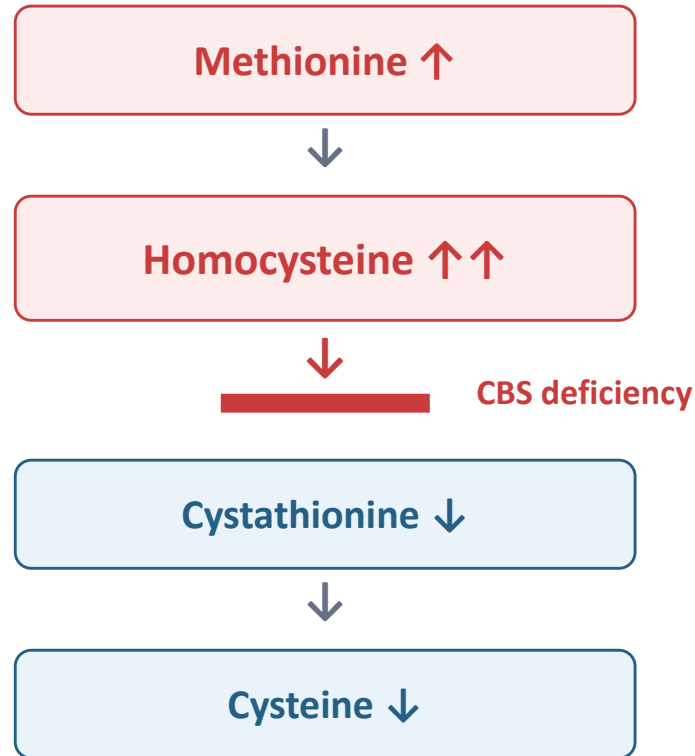
TYPE 1

CBS deficiency: transsulfuration is blocked

Homocysteine cannot be efficiently converted to cystathionine

WHAT GOES WRONG

- CBS is the first enzyme of transsulfuration
- The blocked route traps sulfur upstream
- Cysteine becomes conditionally essential



BIOCHEMICAL FINGERPRINT

tHcy	↑↑
Methionine	↑
Cystathionine	↓
MMA	Normal

WHY IT CAUSES DISEASE

Homocysteine toxicity → thromboembolism • ectopia lentis • skeletal overgrowth • CNS involvement

TYPE 2

MTHFR deficiency: the folate methyl donor is missing

Low 5-methyl-THF impairs remethylation of homocysteine to methionine

WHAT GOES WRONG

- MTHFR cannot generate enough 5-methyl-THF
- Methionine synthase lacks its methyl donor
- Methionine and SAM synthesis fall

5,10-Methylene-THF



MTHFR deficiency

5-Methyl-THF ↓



Methionine synthase

Homocysteine ↑↑ → Methionine ↓



MAT I/III

SAM ↓ → methylation capacity ↓

BIOCHEMICAL FINGERPRINT

tHcy

↑↑

Methionine

↓

5-Methyl-THF

↓

MMA

Normal

WHY IT CAUSES DISEASE

Low methionine/SAM plus homocysteine toxicity → developmental, neurologic, psychiatric and thrombotic disease

TYPE 3

cbIE/cbIG: methionine synthase cannot function

An isolated methylcobalamin-dependent remethylation defect

WHAT GOES WRONG

- cbIG (MTR): methionine synthase is defective
- cbIE (MTRR): the enzyme cannot be reactivated
- The methylmalonyl-CoA pathway remains intact

Homocysteine ↑↑



5-methyl-THF + MeCbl



**MTR / MTRR
defect**

Methionine ↓ or normal



MAT I/III

SAM ↓ → methylation capacity ↓

BIOCHEMICAL FINGERPRINT

tHcy	↑↑
Methionine	↓ / N
MMA	Normal
Macrocytosis	May occur

WHY IT CAUSES DISEASE

Impaired methionine/SAM production → neurologic decline, developmental or psychiatric disease; thrombosis may occur

TYPE 4

Combined cobalamin defects: two pathways fail together

cbLC and related defects impair both methylcobalamin and adenosylcobalamin metabolism

WHAT GOES WRONG

- Intracellular cobalamin processing is impaired
- MeCbl deficiency blocks remethylation
- AdoCbl deficiency blocks methylmalonate disposal

Intracellular cobalamin-processing defect



MeCbl ↓
Methionine synthase ↓

AdoCbl ↓
Methylmalonyl-CoA mutase ↓



tHcy ↑↑
Methionine ↓ / N

MMA ↑↑
C3 may rise

FINGERPRINT

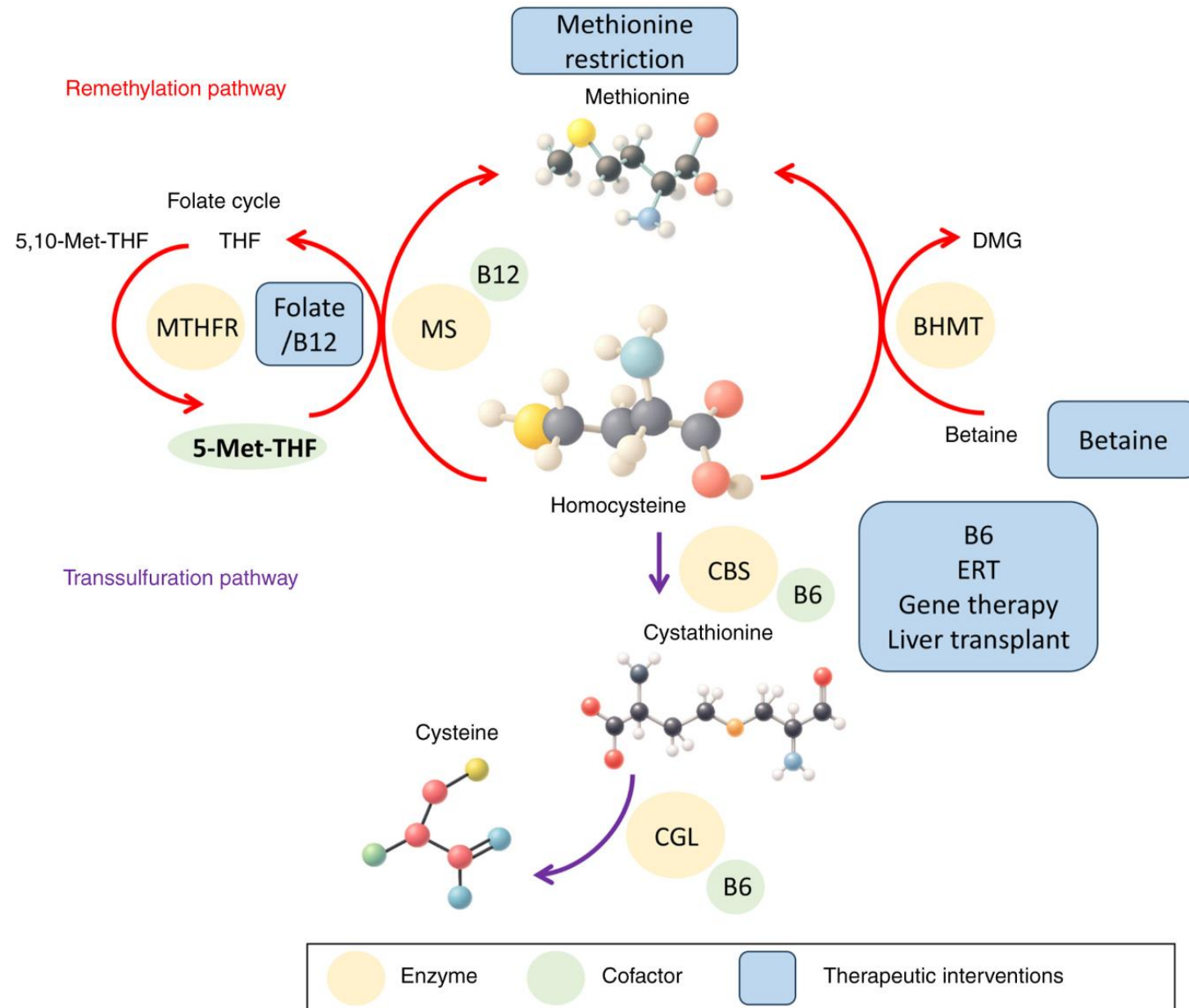
tHcy ↑↑
Met ↓ / N
MMA ↑↑
C3 ↑

WHY IT CAUSES DISEASE

Combined homocysteine and organic-acid toxicity → neurologic, ocular, hematologic, renal and thrombotic manifestations

Summary: Recommended management for Homocystinuria

Transsulfuration and remethylation pathways



Two vertical bars, one blue and one green, are located on the left side of the slide.

Clinical Feature and Our experiences

Case 1: infection unmasked a treatable remethylation disorder

15-year-old Japanese boy



Clinical trigger: infection converted a slow neurocognitive decline into an acute neuropsychiatric crisis.

High tHcy plus low methionine localized the block

229.9
tHcy, $\mu\text{mol/L}$

10.9
Methionine, $\mu\text{mol/L}$

Normal
Urinary MMA

**Remethylation
defect**

Phenotype

- Psychosis and recurrent seizures
- Spastic paraparesis
- Periventricular white-matter disease

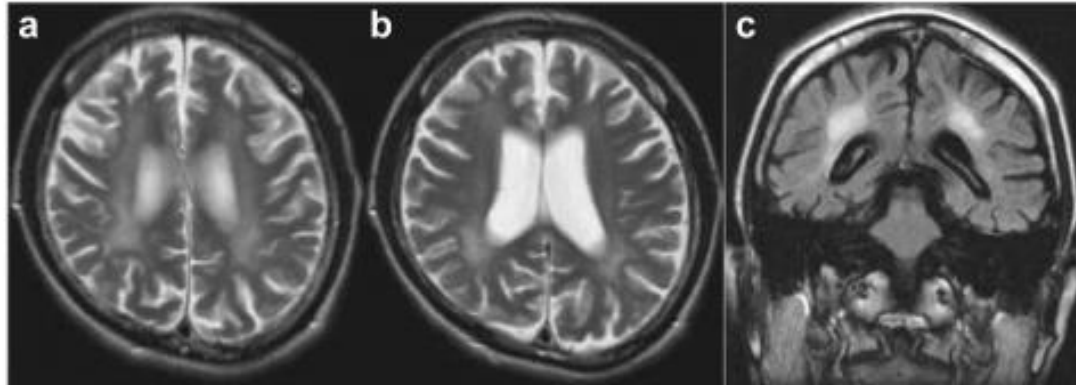
Confirmation

- Compound heterozygous MTHFR variants
- Residual activity: 2.8 nmol/h/mg
- Control mean: 25.3 ± 8.9

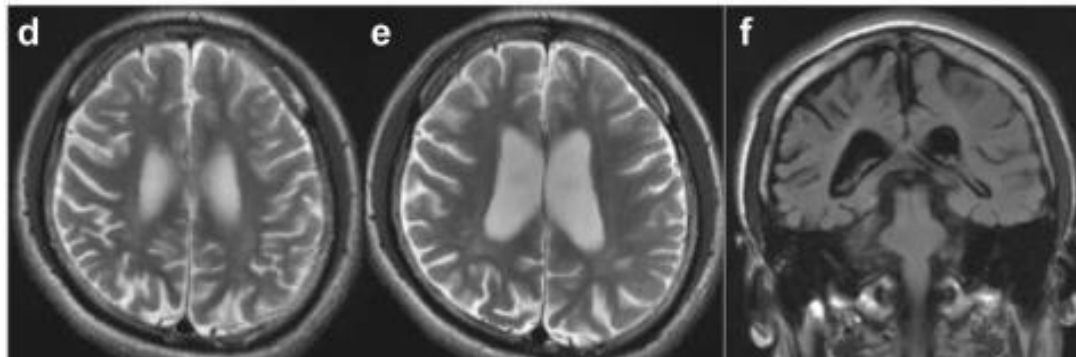
A negative newborn screen did not exclude late-onset cblC.

Betaine reversed biochemical and MRI abnormalities

Before



8 months later



Betaine
3 g/day → 9 g/day

229.9 → 91.2
tHcy, $\mu\text{mol/L}$

10.9 → 20.4
Methionine, $\mu\text{mol/L}$

Psychosis resolved • mobility improved • no relapse at 2 years

Case 2: pulmonary hypertension and aHUS exposed cblC

Previously healthy 2-year-old boy

- One month of fatigue and poor appetite
- Tachypnea 60/min and oxygen saturation 85%
- Palmo-plantar edema, cyanosis and anasarca
- Systemic hypertension and rapid deterioration

Cardiopulmonary crisis

**Estimated pulmonary
pressure
107 mmHg**

**Right-ventricular enlargement
+ thrombotic microangiopathy**

A negative newborn screen did not exclude late-onset cblC.

High tHcy plus MMA identified a combined cobalamin defect

High

tHcy

High

Methylmalonic acid

Low

Methionine pattern

**Think
cblC**

Why this matters

- PAH + aHUS/TMA can be metabolic
- Serum B12 may be normal
- Treatable multisystem disease

Confirmation

**MMACHC compound heterozygosity
c.271_272dupA / c.347T>C**

The biochemical triad—not the serum B12 level—should trigger treatment.

Combination therapy rapidly reversed the cblC crisis

Metabolic treatment

IM hydroxocobalamin 1 mg/day
+
Oral betaine 250 mg/kg/day
+
Folinic acid + carnitine

After 15 days

20
tHcy, $\mu\text{mol/L}$

0.92
MMA, $\mu\text{mol/L}$

Cardiac and systemic symptoms
improved dramatically

At 2 years: normal development, normal echocardiogram, tHcy 11.6 $\mu\text{mol/L}$.

Betaine was adjunctive; parenteral hydroxocobalamin remained the cornerstone.

Case 3: thrombosis revealed classical homocystinuria

6-year-old boy with speech and developmental delay

344

tHcy, $\mu\text{mol/L}$

64

Methionine, $\mu\text{mol/L}$

At 6.5 years

**Raised intracranial pressure
+
Superior sagittal sinus
thrombosis**

CBS variant reported: c.919G>A (p.G307S)

The vascular event was the first major acute complication.

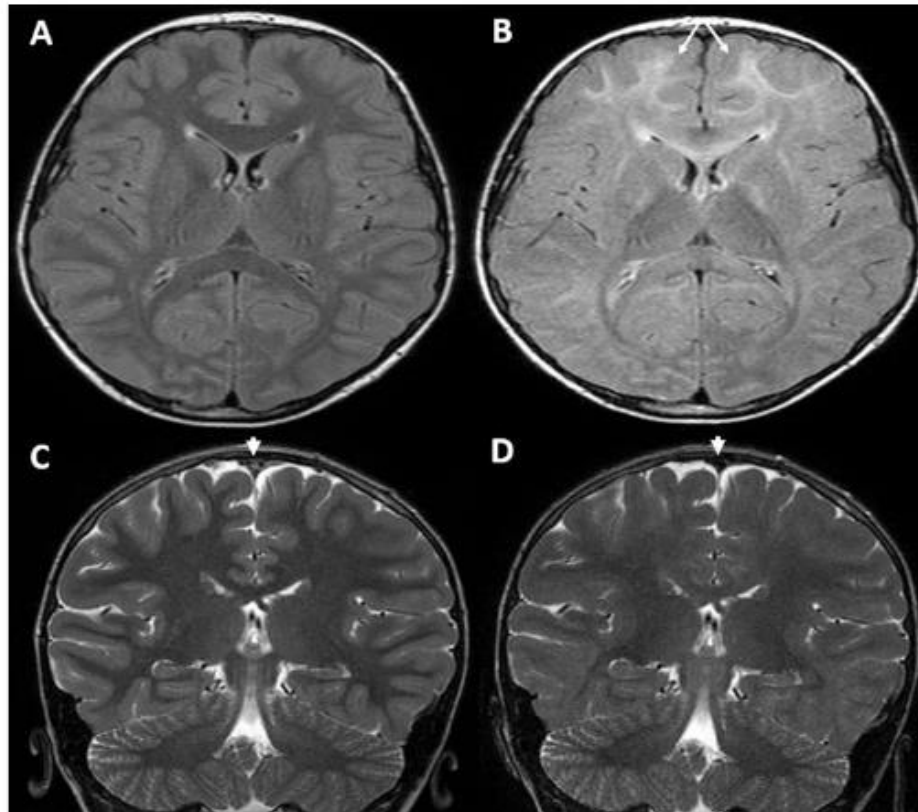
tHcy fell while methionine rose dangerously



*The publication reports betaine hydrochloride; this is not interchangeable with pharmaceutical-grade betaine anhydrous.

In CBS deficiency, methionine is the safety biomarker.

Dietary control reversed the neurologic and MRI changes



After 3 months

1,285 → 233

Methionine, $\mu\text{mol/L}$

Weakness resolved

**Cognition, speech and motor skills
improved**

White-matter changes resolved

**Monitor methionine and diet whenever
betaine is used in CBS deficiency.**

Management with **CYSTADANE®** | **BETAINE ANHYDROUS**

based on Guidelines

E-HOD

And Local

International disease-specific guidelines are primarily provided by E-HOD, while ACMG and Japanese guidelines provide region-specific newborn-screening and clinical-practice recommendations.

The same drug has three different clinical jobs

CBS deficiency

Adjunct to lower tHcy

Watch methionine

Severe MTHFR deficiency

Core, disease-modifying therapy

Start early

Cobalamin disorders

Partner to parenteral OHcbl

Restore Met; lower tHcy

Today's goal: prescribe by pathway—not by the label “homocystinuria.”

Read methionine before naming the pathway

Markedly elevated plasma total homocysteine (tHcy)

High / high-normal Met

Think transsulfuration

CBS deficiency

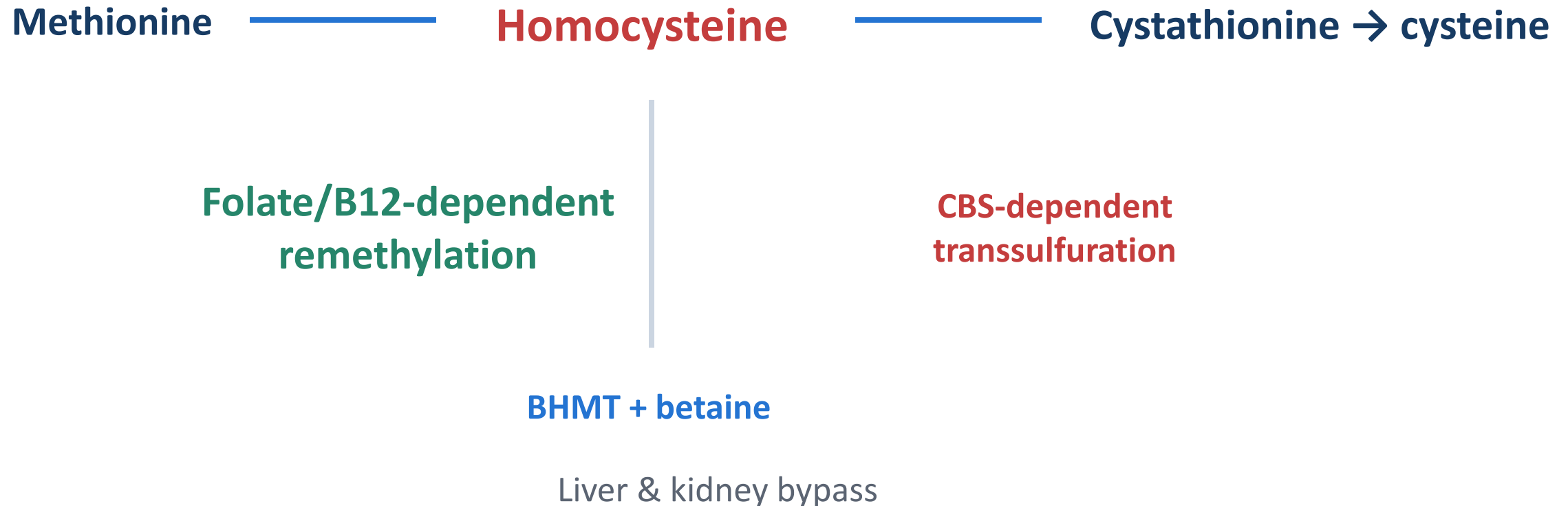
Low / low-normal Met

Think remethylation

MTHFR / cbl defects

Add MMA: elevated in combined cobalamin defects; normal in isolated remethylation defects.

Two exits from homocysteine determine phenotype and treatment



Cystadane creates a metabolic bypass—not a cure

Betaine

+

Homocysteine

BHMT

↓ tHcy

Benefit

↑ Methionine

Trade-off

A broad indication supported by rare-disease evidence

EU indication

Adjunctive treatment of homocystinuria due to CBS, MTHFR or cobalamin cofactor defects

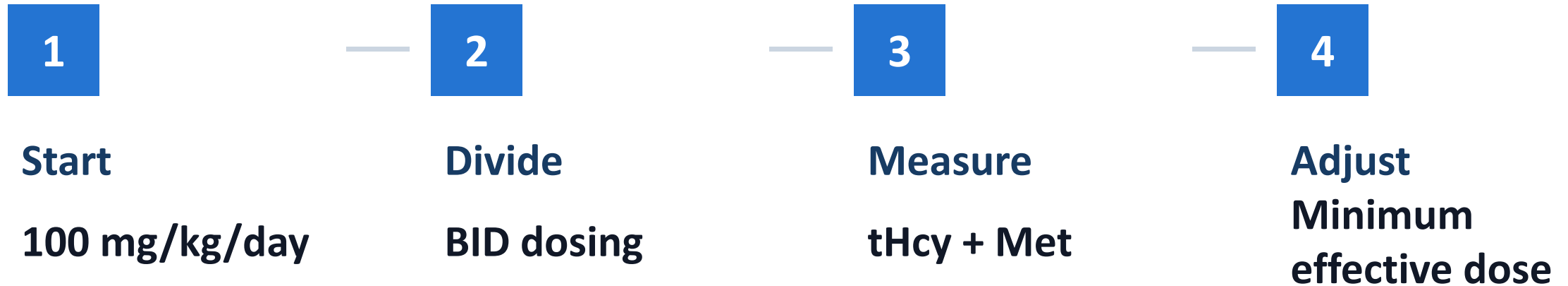
What supports use

- Consistent biochemical response
- Observational cohorts and case series
Strong outcome signal in severe MTHFR
- deficiency

What remains uncertain

- No randomized efficacy trials
- Dose–response varies by pathway
- Clinical endpoints lag behind tHcy

Start simple: twice daily, then titrate to biochemical response



EMA: 100 mg/kg/day in 2 doses; some patients require >200 mg/kg/day.
US label: usual 6 g/day (3 g BID); up to 20 g/day has been used.

Always follow the locally approved label and specialist protocol.

Administration: make adherence easier

1

Measure

Use the supplied scoop or a validated gram scale

2

Mix

Water, juice, milk, formula—or soft food

3

Take now

Dissolve/mix immediately before ingestion

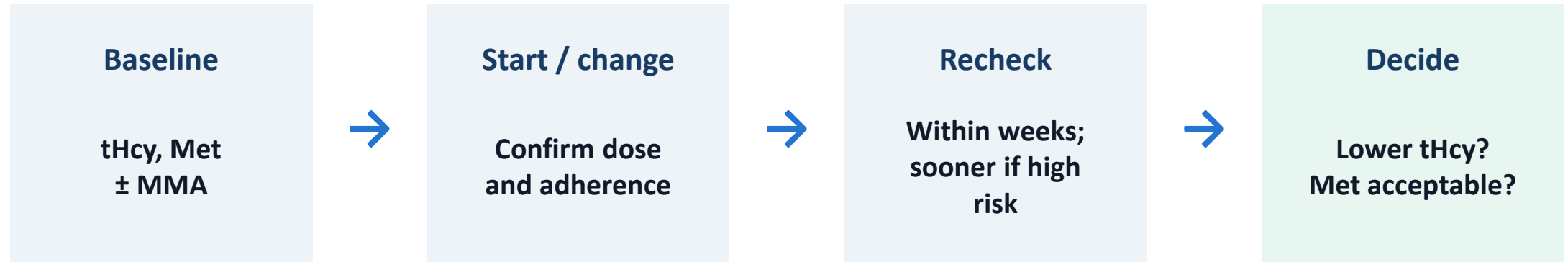
4

Repeat

Link BID dosing to stable daily routines

Do not substitute betaine hydrochloride supplements for pharmaceutical-grade anhydrous betaine.

A titration loop is safer than a fixed “maximum dose”



CBS deficiency: do not up-titrate without reviewing methionine.

CBS deficiency: betaine is usually adjunctive

First define B6 responsiveness

- Pyridoxine-responsive: optimize pyridoxine ± folate/B12
- Pyridoxine-unresponsive: methionine restriction + cystine
- Add betaine when tHcy target is not achieved

Why betaine alone may fail

Homocysteine → methionine

**Rising Met can reduce
biochemical response and
create safety risk**

Goal: prevent vascular events by sustained metabolic control.

CBS targets depend on pyridoxine response

Fully B6-responsive

Aim tHcy <50 µmol/L

Often achievable with pyridoxine
± folate/B12

B6-unresponsive / partial

Aim tHcy <100 µmol/L

Diet + cystine ± pyridoxine
+ betaine as needed

If <100 is unattainable, keep tHcy as low as safely possible.

In CBS deficiency, methionine is the safety biomarker

Betaine



Methionine ↑



Cerebral edema

Red flags

- Morning headache • vomiting • visual change
- Behavioral change • altered consciousness • seizures

Keep plasma Met <1,000 µmol/L; reassess dose and diet well before extreme values.

Stop betaine and urgently evaluate if cerebral edema is suspected.

Severe MTHFR deficiency: early betaine changes survival

Treatment of choice

Start immediately

Typical reported doses

Children 100–250 mg/kg/day

Adults 5–20 g/day

EARLY

↓ mortality

Preserves neurodevelopment

**Do not wait for molecular confirmation
when the biochemical pattern is
compelling.**

Cobalamin defects require two complementary bypasses

Parenteral hydroxocobalamin

Restores intracellular
cobalamin-dependent pathways

Mainstay therapy

+

Oral betaine

BHMT bypass lowers tHcy
and raises methionine

Adjunctive synergy

In combined defects, follow MMA as well as tHcy and Met.

Do not impose a CBS diet on a remethylation disorder

CBS deficiency

**Restrict methionine
when indicated**

Remethylation defects

**Maintain methionine
in the normal range**

Protein restriction and methionine-free medical foods are contraindicated in cblC and other remethylation disorders.

Avoid nitrous oxide: it inhibits methionine synthase.

Monitoring must answer efficacy, safety and adherence

Measure	Who	Why it matters
tHcy	All disorders	Primary biochemical response
Methionine	All; critical in CBS	Benefit in RD / safety in CBS
MMA	Combined cbl defects	Cobalamin-pathway response
B12, folate	All	Correct cofactor deficiency
Clinical review	All	Neuro, eye, vascular, renal, growth
Dose + intake	All	Adherence and administration

Treat first when remethylation disease is clinically plausible

- Neonatal encephalopathy / poor feeding
- Developmental regression or seizures
- Psychiatric change or unexplained myelopathy
- Thrombosis, TMA or pulmonary hypertension
- Macular disease ± elevated MMA

Before confirmation

**Draw tHcy, Met, MMA,
B12 and folate**

**Then start appropriate urgent
therapy**

A normal serum B12 does not exclude an intracellular cobalamin disorder.

Three cases—three prescriptions

A

tHcy 220
Met 180

CBS deficiency

Diet + B6 trial
Add betaine if needed

B

tHcy 180
Met 8; MMA normal

Severe MTHFR

Start betaine now

C

tHcy 160
Met 10; MMA ↑

cbIC

Parenteral OHcbl
+ betaine

The methionine/MMA pattern determines what betaine must be paired with.

A five-question prescribing checklist

1 Which pathway is blocked?

2 What therapy must accompany betaine?

3 What is the tHcy goal?

4 Is methionine therapeutic—or dangerous?

5 When will I recheck and escalate?

TAKE-HOME from EMA/E-IOD/Japan Guideline

One reaction.

Three disease-specific strategies.

CBS

Adjunctive; combine with diet/B6 strategy; monitor Met **under betaine**

Detectable by NBS

MTHFR

Start early—**betaine is core** disease-modifying therapy

Cannot detectable by NBS

cbl defects

Combine with parenteral hydroxocobalamin; follow MMA

Treat the pathway • titrate to tHcy and Met • protect the brain