

Table

Clinical and laboratory data of patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	18	9	14	35	21
Sex	M	F	M	F	M
Growth failure	<3rd percentile	<3rd percentile	<3rd percentile	Normal	Normal
Hepatosplenomegaly	Yes	Yes	Yes	Yes	Yes
Dermatological symptoms	Vasculitis	None	None	Vasculitis, eczema	Vasculitis, furuncles ulcers
Rheumatic symptoms	Arthritis	Arthritis	Arthritis	Arthritis, uveitis	Arthritis
Plasma C-reactive protein (mg/L)†	41-143	100-200	22	17	45-146
Haemoglobin (g/L)	80	90	109	125	80
Total white-cell counts (10 ⁹ cells/mL)	2-0	3.7-5.0	1.5	5.0	3.8
Monocytes	0		1.9%	1.9%	4.3%
Plasma zinc (mol/L)‡	180-200	82-96	160-200	175	77
Plasma calprotectin (g/L)§	6.5	1.4, 2.55	9	6.1	1.5

†Reference <10 mg/L. ‡Reference 10-18 mol/L. §Reference <1 mg/L

Adapted from Sampson B, et al. *Lancet* 2002;360:1742-1745.

hypothesis regarding "functional zinc deficiency" remains unproven. Since calprotectin is a calcium binding protein, it would have been of interest to report total and ionized calcium values in these patients.

Zinc deficiency may be congenital or acquired. Acrodermatitis enteropathica (OMIM 201100) is an autosomal recessively transmitted disease characterized by bullous lesions of the skin, alopecia, diarrhea, and growth failure with hypozincemia. Administration of supplemental zinc ameliorates these abnormalities. Approximately 50% of patients with acrodermatitis enteropathica have a loss-of-function nonsense or missense mutation in SLC39A4 (Solute Carrier Family 39 [Zinc Transporter], Member 4) encoding a renal- and intestine-specific transmembrane zinc transporter protein (OMIM 607059, chromosome 8q24.3). Zinc deficiency may be acquired due to dietary

deficiency, decreased absorption due to co-ingestion of zinc-binding materials such as clay or phytates, malabsorption as in patients with chronic inflammatory bowel disease, or excessive excretion as in patients with sickle cell disease and hyperzincuria.

Allen W. Root, MD

Second Editor's Comment: *I am puzzled by the possibility of copper deficiencies in these patients. The clinical picture and the anemia and leucopenia are typical of it. A deficit of this mineral would not likely result in a deficiency of Ca/Zn SOD (super oxidase desmutase) though I do not know of studies of its effects on calprotectin.*

Fima Lifshitz, MD

Initial Treatment Dose of L-Thyroxine in Congenital Hypothyroidism

The American Academy of Pediatrics (AAP) recommends an initial L-thyroxine dose of 10 to 15 mcg/kg/d for the treatment of congenital hypothyroidism (CH).

Several studies have shown that early high dose therapy which quickly produces serum T-4 levels within the "normal" neonatal range may be associated with the

development of near normal IQ scores; whereas therapy with lower dosages are associated with a delay in achieving normal T-4 concentrations by as little as 1 week may result in lower IQ scores. Thus, pediatricians and pediatric endocrinologists need to be familiar with treatment regimens that achieve the T-4 goal with as little delay as possible, yet do not produce untoward side effects such as craniosynostosis.

Selva and colleagues present data obtained in 47 congenitally hypothyroid neonates (BW 3-4kg) using a prospective randomized study of 3 different L-thyroxine dosing regimens (Group 1 – 37.5mcg/d; Group 2-loading dose 62.5mcg/d x 3d, then 37.5mcg/d; Group 3 – 50mcg/d). Serum T-4, free T-4, T-3, free T-3, and TSH were measured at baseline, 3 days, and 1, 2, 4, 8, and 12 weeks after starting treatment. No changes in treatment dose were made for 2 weeks. At that time, dosages were altered using the following important algorithm to maintain serum T-4 concentrations between 10 – 15 mcg/dL; a) T-4 < 8.5mcg/dL, increase dose by 12.5mcg/d, b) T-4 between 8.5 and 9.9mcg/dL, increase dose by 6.25mcg/d, c) T-4 between 15.1 and 16.5mcg/dL, decrease dose by 6.25mcg/d, d) T-4 greater than 16.5mcg/dL, decrease dose by 12.5mcg/d.

Pre-treatment thyroid levels were similar in all three groups. Infants in Groups 2 and 3 achieved target T-4 levels by 3 days, while infants in Group 1 did so by 1 week of age. Subjects in Group 3 had T-4 levels above 16mcg/dL by 1 week, while the others were in the target range at both 1 and 2 weeks. TSH remained elevated in Groups 1 and 2 for the first 2 weeks. After 2 weeks, serum T-4 remained within the target range in all three groups, but doses were adjusted as outlined above. At 12 weeks, mean L-thyroxine dose was 36.7 mcg/d (approximately 6mcg/kg/d) in all groups, which was associated with ideal target levels of T4, T3, and TSH. Free T-4 levels rose above normal by 1 week and remained above normal at 12 weeks in all age groups. There were no significant differences in TSH concentrations at 12 weeks among the groups.

When patients were divided into severe and moderate CH categories based on serum T-4 above or below the median value, the differences in initial T-4 levels were abolished by 3 days for Group 3 infants and by 1 week for the others.

The authors state that their data shows that a loading dose of 62.5mcg/d x3 days followed by a dose of 37.5mcg/d raises serum T-4 levels quickly but does not normalize TSH levels. However, the sustained dose of L-thyroxine (50mcg/d – Group 3) normalized TSH levels within 2 weeks and abolished any difference in serum T-4 levels between severe and moderate CH infants by 3 days. Consequently, they recommend the use of a higher target range of 10 to 18mcg/dL for T-4 for the first

2 weeks of therapy to insure that the benefits of therapy are maximized.

Selva K, et al. *J Pediatr* 2002;141:786-792.

Editor's Comment: *It may seem surprising to read a paper dealing with the "correct" L-thyroxine dose for treating infants with CH, when most neonatal screening programs have been in place for approximately 20 years and have been highly successful in identifying these infants and seeing that they receive what has been considered "appropriate" treatment. However, the medical community, despite well-delineated guidelines from the AAP, has yet to define "appropriate" treatment. The article by Selva et al helps clarify three different treatment regimens. They are to be commended for the prospective randomized protocol followed. It is interesting that they refrain from "recommending" a single or favorite regimen. Indeed all three regimens work well if the goal is to normalize serum T-4 within 1 week. Quicker attainment of the target range requires a loading dose for three days. The accompanying algorithm for adjusting L-thyroxine doses is helpful and all of these data and recommendations need to be disseminated to those caring for neonates.*

William L. Clarke, MD

Second Editor's Comment: *This detailed analytical study is accompanied by a detailed analytical report pointing out that several groups have demonstrated as much as a 20 point IQ deficit in severely affected CH infants who did not have rapid and complete conversion of serum hormonal levels of T4, T3, free T4 and T3, and TSH to normal. The article convinced me that a treatment protocol as used for group 3 is currently the best available.*

In an accompanying editorial by Dr. Nancy Hopwood¹ of the University of Michigan, emphasis is given to the importance of using only tablets of T4 because liquid preparations may be unreliable. She also points out that persistent TSH elevation can result from faulty absorption of T4 in patients with milk allergy, malabsorption of various causes, with soy formulas, iron therapy, and with acidic juices in children of all ages. The article by Selva et al and the editorial by Dr. Hopwood fit together splendidly.

Reference

1. Hopwood NJ. *J Pediatr* 2002;141:752-4.

Robert M. Blizzard, MD