Immune Recovery of Malnourished Children Takes Longer than Nutritional Recovery: Implications for Treatment and Discharge

by P. Chevalier,* R. Sevilla,** E. Sejas,** L. Zalles,** G. Belmonte,** and G. Parent*
* Laboratoire Nutrition Tropicale, ORSTOM, BP 5045, 34032 Montpellier Cedex, France
**IIBISMED, Facultad de Medicina, UMSS, Casilla 3119, Cochabamba, Bolivia

Summary

Protein-energy malnutrition decreases cellular immunity yet immune recovery has rarely been investigated during nutritional rehabilitation. Malnourished children from low income families of Cochabamba (Bolivia) were hospitalized for 2 months in the Center for Immune and Nutritional Rehabilitation (CRIN), of the German Urquidi Materno-Infantil Hospital. They received a special four-step diet. Nutritional status was determined by a daily clinical examination and weekly anthropometric measurements. Immune status was assessed by weekly ultrasonography of the thymus. The classical criterion for discharge (90 per cent of median reference weight for height) was reached after the first month, whereas a 2-month period was required for complete immunologic recovery. The children belonged to disadvantaged population groups with high exposure to disease. In such an environment, discharge based only on nutritional status after 1 month of treatment could explain frequent relapses because the children were still immunodepressed.

Introduction

The treatment of severe protein-energy malnutrition (PEM) implies clinical recovery, nutritional rehabilitation, and prevention of relapse.[1] Since the report on diet for nutritional rehabilitation by Waterlow,[2] the classical treatment of PEM has been based on appropriate protein-energy supplements[3] in nutritional rehabilitation centers.[4] The nutritional treatment of severe PEM is now commonly agreed,[5] but many centers still cannot reduce the high case–fatality rates of severe PEM.[6]

The criteria for recovery and discharge are based on anthropometric parameters.[5] These criteria were confirmed by the last WHO draft on management of severe malnutrition: 'the most important requirement for discharge is that the child's weight for height has reached 90 per cent of median reference values'.[7] Nevertheless, the weight-for-height relationship as an indicator of nutritional recovery and the anthropometric criterion of discharge does not coincide with the recovery of physiological parameters.[8] For instance, severe malnutrition has a strong effect on mental development[9-11] but few centers incorporate psychosocial stimulation in the treatment of severely malnourished children. Likewise, impaired cellular immunity in malnourished children is well known[12] but immune recovery was rarely considered during nutritional rehabilitation, even though malnourished children are particularly sensitive to opportunistic infections. Parent et al.[13] noted that 'biochemical parameters were back to normal within 20 days while the return to normal of the immunological indices was more protracted'.

Severely malnourished children belong to disadvantaged population groups whose exposure to disease is high. After discharge, they return to the same pathogenic environment and the risk of relapse is increased.

To avoid or minimize frequent relapses and the failure of nutritional recovery programmes, we proposed to assess nutritional immunodeficiency and to stimulate immune rehabilitation to lessen the lag between nutritional and immune recovery.

Patients and Methods

One hundred and ten severely malnourished children, aged a mean of 16.9 months, were selected from children hospitalized in the German Urquidi Materno-Infantil Hospital in Cochabamba (Bolivia). The were admitted to the CRIN (Center for Immune and Nutritional Rehabilitation) for a 2 month follow-up study, with parental and hospital ethical committee consent. Most of them came from poor homes in Cochabamba suburban areas.

Kwashiorkor, marasmus, and combined PEM diagnoses were based on weight for height,[14] arm/head circumferences ratio,[15] and clinical findings such as presence of oedema, loss of subcutaneous tissue, and diminished muscle mass.[16]

Correspondence: Ph Chevalier, Laboratoire Nutrition Tropicale, ORSTROM, BP 5045, 34032 Montpellier Cedex, France. Tel. 00 33 4 67 41 61 92; Fax. 00 33 4 67 54 78 00. E-mail chevalie@mpl.orstom.fr

TABLE 1
Evolution of anthropometric indices during 9-week treatment period (mean ± SD)

Week	n	HAZ[a]	WHZ[b]	WHM[c]
0	92	−3.20 ± 1.35	−2.33 ± 0.98	78.4 ± 8.5
1	99	−3.27 ± 1.32	−2.22 ± 1.09	79.6 ± 9.6
2	95	−3.32 ± 1.36	−1.81 ± 1.11	83.4 ± 9.7
3	98	−3.31 ± 1.35	−1.46 ± 1.11	86.6 ± 9.9
4	95	−3.30 ± 1.31	−1.15 ± 1.07	89.5 ± 9.6
5	96	−3.23 ± 1.21	−0.95 ± 1.00	91.4 ± 9.1
6	94	−3.29 ± 1.35	−0.78 ± 0.95	93.0 ± 8.6
7	92	−3.22 ± 1.27	−0.67 ± 0.97	94.0 ± 8.9
8	91	−3.22 ± 1.27	−0.59 ± 0.93	95.0 ± 8.5
9	79	−3.16 ± 1.34	−0.52 ± 0.94	95.4 ± 8.6

[a] HAZ: Height for age (z-score).
[b] WHZ: Weight for height (z-score).
[c] WHM: Weight for height (% median).

The children received the four-step diet over 2 months, as follows:

- Initial phase (1 week): a milk-based diet with fifty per cent lactose,[17] distributed in seven feeds/day and supplying 1.5–2.5 g of protein and 120–150 kcal/kg body weight/day, according to the PEM pattern.

- Transition phase (1 week): gradual and slow increase in protein and energy.

- 'Caloric-protein bombing' phase (6 weeks): 5 g of protein and 200 kcal/kg body weight/day.[18,19]

- Discharge preparation phase (1 week): gradual decrease in protein and energy.

After CRIN admission, each child received a clinical examination daily. Weight, height, arm and head circumferences, and triceps skinfold thickness were measured weekly according to standardized the methods of Jelliffe[20] and Frisancho.[21] Weight for age, height for age, and weight for height were calculated using the CDC *Anthro* software.[22] Arm/head circumferences ratio was calculated according to the Kanawati–McLaren index[15] and the upper arm bone–muscle area according to Frisancho.[21] With reference to the last WHO draft on management of severe malnutrition,[7] 90 per cent of median weight for height was the anthropometric criterion for discharge.

Mediastinal ultrasonography using an echo camera (Aloka SSD-210 DXII, Tokyo) and a 5 MHz linear paediatric probe was done weekly. The standardized area of the ultrasonographic image of the left thymus lobe between the second and fourth ribs is significantly correlated with T-lymphocyte subpopulations and is used as a non-invasive method for immunological assessment.[23–25] In a previous study,[26] the average standardized thymic area (STA) was 350 mm^2 for Bolivian control children who were apparently 'healthy' with weight for height and height for age above 90 per cent of median reference values. This STA was used as the cut-off point for thymic recovery.

Results

Table 1 presents the evolution of the anthropometric parameters used for the Waterlow classification.[14] Height for age during the 2-month period did not change. On weight for height, malnourished children exceeded the threshold for malnutrition (−2 SD) between the first and second weeks after admission. At a threshold for discharge of −1 SD, the children exceeded the cut-off point between the fourth and fifth weeks after admission. When the results were expressed as a percentage of the weight for height reference median (WHM), the threshold for malnutrition (80 per cent) and the threshold for discharge (90 per cent) were exceeded within the same periods as above (Fig. 1).

Table 2 presents the evolution of the mid upper arm circumference (MUAC), the upper arm muscle area (UAMA), and the arm circumference–head circumference ratio (AC/HC) during the 2-month period of nutritional rehabilitation. Values considered normal for those anthropometric parameters[27] were reached only after the second month (Fig. 2).
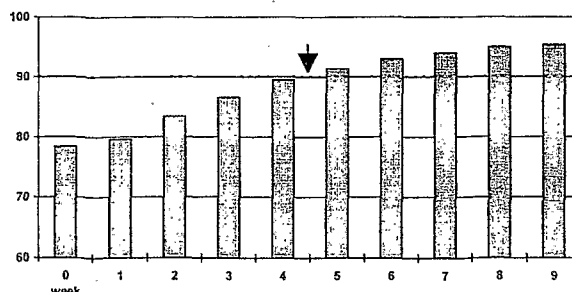

FIG 1. Evolution of weight for height (% median).

TABLE 2

Evolution of anthropometric parameters and standardized thymic area during 9-week treatment period (mean ± SD)

Week	MUAC[a]	UAMA[b]	AC/HC[c]	STA[d]
0	10.8 ± 1.6	7.0 ± 1.8	249 ± 31	70 ± 54
1	11.1 ± 1.8	7.4 ± 2.0	252 ± 43	93 ± 83
2	11.5 ± 1.6	7.7 ± 1.9	262 ± 29	140 ± 100
3	11.8 ± 1.7	8.1 ± 2.0	270 ± 31	175 ± 118
4	12.4 ± 1.7	8.7 ± 2.1	281 ± 32	193 ± 116
5	12.7 ± 1.7	9.1 ± 2.1	287 ± 30	222 ± 126
6	12.8 ± 1.7	9.1 ± 2.2	290 ± 30	250 ± 149
7	13.1 ± 1.6	9.6 ± 2.1	297 ± 28	292 ± 148
8	13.4 ± 1.6	9.9 ± 2.3	301 ± 28	324 ± 153
9	13.5 ± 1.7	10.0 ± 2.3	302 ± 29	376 ± 150

[a] MUAC: mid upper arm circumference (cm).
[b] UAMA: upper arm muscle area (cm^2)
[c] AC/HC: (arm circumference/head circumference)$\times 10^3$.
[d] STA: standardized thymic area (mm^2).

Malnourished children reached and exceeded the threshold value for thymic recovery (350 mm^2) between the eighth and ninth weeks (Fig. 3).

Discussion

Impaired cellular immunity[28,29] with thymic involution[30] or nutritional thymectomy[31] are the main characteristics of immune deficiency secondary to malnutrition. Thymic ultrasonography, a non-invasive technique, enabled us to check the thymus gland weekly and provided direct evidence of nutritional thymic involution and progressive recovery during nutritional rehabilitation.

Figures 1 and 3 show that nutritional recovery was faster than immune recovery. Anthropometric criteria for discharge were reached in 5 weeks whereas 9 weeks were needed for similar immunologic recovery as revealed by thymic echography.

This lag between nutritional and immune recoveries means that malnourished children, fit for discharge when they reached the anthropometric cut-off points, remained immunodepressed. The principal consequence is impaired host resistance to infections, which is responsible for high morbidity and mortality rates.

The children admitted to the CRIN belong to disadvantaged sections of the population characterized by low income families, crowded living conditions, and lack of sanitation. Such an environment, where exposure to disease is greatest, operates as a 'PEM generator'. Discharge based on weight-for-height recovery and return to the same environment could explain the frequent relapse of 'recovered children' and the failure of PEM treatments that include only nutritional recovery.

However, some anthropometric parameters based on brachial measurements such as MUAC reach normal values only after the second month (see Fig. 2). When children reached the threshold for weight-for-height recovery (after 1 month), the MUAC value was 12.5 cm, which is considered the threshold between severe and moderate malnutrition.[27]

Unlike WHM, MUAC and STA presented similar kinetics of recovery and confirmed previous observations on better STA–MUAC than STA–WHM correlations in apparently 'healthy' Bolivian children (unpublished data). The lag between WHM and MUAC recoveries and the analogy between STA and MUAC recoveries were consistent with the observation of Briend on the greater risk of dying if the MUAC is low.[32]
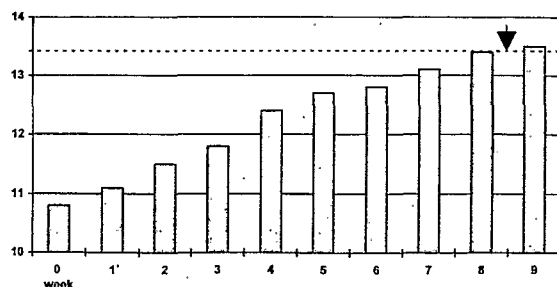

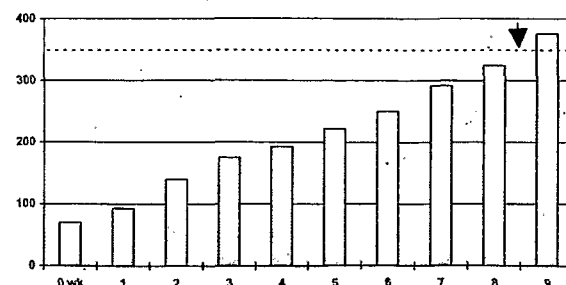FIG. 2. Evolution of mid upper arm circumference (mm^2).

FIG. 3. Evolution of thymic area (mm^2).

To prevent frequent relapses and to reduce the high case–fatality rates observed in many rehabilitation centers, practitioners should consider immune recovery as part of the management of severe malnutrition. Moreover, similar periods of recovery for STA and MUAC can also be to used to assess complete recovery.

Complete rehabilitation of children suffering from severe PEM implies a long-stay treatment; immunostimulating factors should be used to reduce the time required for immune recovery. A previous study[33] showed that physiological doses of zinc supplement during the 2-month CRIN hospitalization significantly reduce the immune recovery period. Anthropometric and immune recoveries coincide and the children could be discharged after only 1 month of hospitalization, to face a pathogenic environment with confidence.

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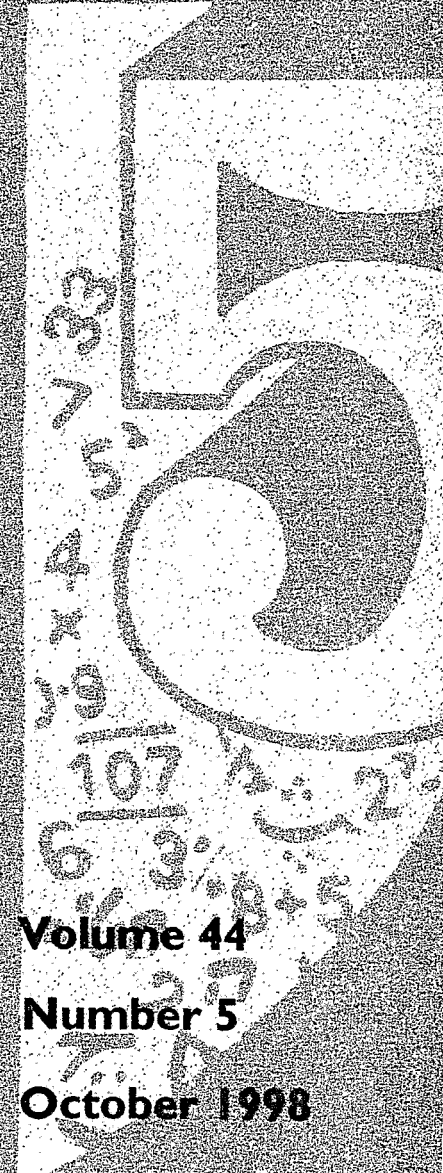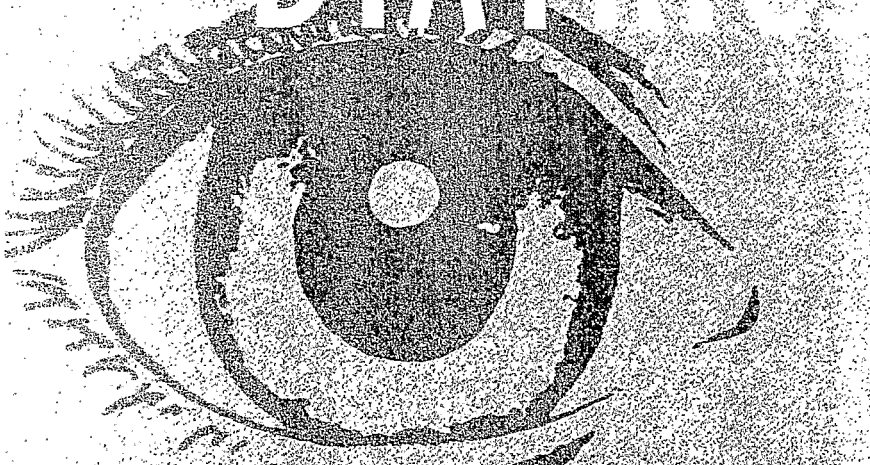
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