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Chapter 7

Acute malnutrition is common in Malawian patients with a Wilms tumour; a role for “peanut butter”?

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Abstract

**Background:** Children with cancer in resource limited countries are often malnourished at diagnosis. Acute malnutrition is associated with more infectious complications and an increased risk of morbidity and mortality in major surgery.

**Methods:** All new patients with the clinical diagnosis of a Wilms tumour admitted in the Queen Elizabeth Central Hospital, Blantyre, Malawi from January 2007 until June 2008 were included. We documented anthropometric parameters, tumour size and serum levels of micronutrients at diagnosis. Corrected weight (body weight – tumour weight) was repeated after 4 weeks of preoperative chemotherapy. During therapy oral feeds were encouraged and a locally made ready to use therapeutic peanut butter-based food (chiponde) supplied.

**Results:** A high rate of acute malnutrition was found in patients with Wilms tumour at diagnosis (45-55%), much higher than in community controls (11%). Patients (40%) and community controls (37%) had a similar, high rate of stunting (low height for age), a sign of chronic malnutrition. Tumour size at diagnosis and the degree of acute malnutrition at diagnosis was correlated; patients with a larger tumour had more severe acute malnutrition (r=-0.88, p <0.01). With a supply of chiponde, seven of 18 patients had a > 5% increase in corrected weight during preoperative chemotherapy. Patients with a more positive nutritional course had a better tumour response to chemotherapy (r =0.52, P <0.05). Surprisingly, few micronutrient deficiencies were found, except for low serum levels of vitamin A (44% of patients).

**Conclusion:** Acute malnutrition, superimposed on chronic malnutrition, is common in patients with Wilms tumour in Malawi. Earlier presentation needs to be encouraged. Chiponde, a peanut butter based ready-to-use-therapeutic-food, is an attractive means of nutritional support which needs further study.
Introduction

The incidence of Wilms tumour is around eight per year per one million children under fifteen years old worldwide [1]. Overall long term survival now exceeds 85% in Europe and North America when management is carried out by a multidisciplinary team [2,3]. However, 80% of children with Wilms tumour live in countries with limited resources where survival is lower [4].

Malnutrition at diagnosis in paediatric cancer patients can be related to the type of tumour and the extent of disease. In Malawi, as in other developing countries, a large proportion of the normal paediatric population is undernourished [4]. We found in a previous study that 55% (70 of 128) of children with cancer admitted in Blantyre, Malawi were acutely malnourished at admission [5].

Wessels et al in a retrospective study described 59 children with Wilms tumour treated in Tijgerberg Hospital, South Africa between 1983 and 1986 [6]. Weight for age (WFA) below the third percentile or weight for height (WFH) less than 90% of the expected value was defined as malnutrition. By these criteria 35% of children (21 of 59) were poorly nourished at diagnosis [6].

There are different ways of evaluating nutritional status. Weight for height is potentially misleading in children with large abdominal tumours that can weigh more than 10% of their total body weight [7]. Arm anthropometry is valuable in these children because it is independent of tumour mass [8].

The relationship between poor nutritional status and a poor prospect for survival in children with cancer has been confirmed in most studies, but not in all [7, 9]. Altered pharmacokinetics, more severe toxicity (neutropenia) and delay of chemotherapy have been reported in children with malnutrition [7,10,11]. The interrelation of malnutrition, diminished immunity and increased risk of infection is well established [7]. This is of great importance in developing countries where the intensity of chemotherapy given is often limited by the level of supportive care. Malnutrition is associated with reduced wound healing and with an increased risk of complications and mortality in major surgery [12].

Micronutrient deficiencies are common in malnourished children, especially zinc and vitamin A deficiency. Vitamin A deficiency is associated with an increased mortality and susceptibility to infections [13]. During childhood, zinc deficiency contributes to stunting and impaired cognitive development and is associated with an increased incidence and prevalence of infectious diarrhoea, pneumonia and malaria [13].

In Malawi, parenteral nutrition is not available. Gastric tube feeding is rarely used, partly because parents are reluctant to accept this approach. This study evaluated the nutritional status at diagnosis and the changes during preoperative chemotherapy of patients with Wilms tumour in Malawi all of whom were supplied with additional nutrition as a peanut based therapeutic ready to use food.
Patients and Methods

All children who presented in the Queen Elizabeth Central Hospital, Blantyre, Malawi from January 2007 until June 2008 with an abdominal mass compatible with the clinical and ultrasound diagnosis of Wilms tumour were included. On admission, the HIV status, age, weight, height, mid-upper-arm-circumference (MUAC), triceps skinfold (TSF) and estimated tumour size were documented. Serum levels of prealbumin, retinol (vitamin A), vitamin E, zinc and magnesium were measured at diagnosis. Corrected weight (body weight – estimated tumour weight) was repeated after 4 weeks of preoperative chemotherapy.

Weight, height, triceps skinfold (TSF) and mid-upper arm circumference (MUAC) were recorded using standard techniques by the same investigator [5]. Arm muscle area (AMA) was extrapolated from the mid upper arm circumference and the triceps skinfold, using the following equation: $AMA = \frac{(MUAC - \pi TS)^2}{4\pi}$ (MUAC in mm, TS is triceps skinfold in mm). Z-scores for height for age (HAZ) and weight for height (WHZ) were derived in reference to the 1978 NCHS growth curve (HANES data) [14]. Results for arm muscle area were compared to the same data set [15]. These results were expressed as below or above the 5th percentile in absence of a standard deviation for this abnormally distributed reference data set.

Tumour size was determined by ultrasound (Aloka 6500 CL). The tumour was measured in three dimensions and the size calculated using the following formula: $volume (ml) = length (cm) \times width (cm) \times height (cm) \times 0.523$ [16]. We assumed, in the calculation of corrected body weight, that the weight of 1 litre of tumour as measured by ultrasonography was 1 kg. Measurements were made at diagnosis and after 4 weeks of treatment.

Preoperative chemotherapy for localized disease consisted of vincristine and actinomycin for four weeks according to SIOP protocols [17]. If metastases were present doxorubicin was added and the period prolonged and regression or resectability of metastases reassessed after 6 and 9 weeks. If metastases were not resectable or had not regressed completely by 9 weeks, preoperative treatment was stopped. Toxicity during chemotherapy was graded daily using the criteria of toxicity of the National Cancer Institute (CTCAE v3.0) and was recorded as a maximum weekly score [18].

Two free meals a day were supplied by the hospital. In addition patients were encouraged to eat one jar (245 gram) of locally made ready-to-use-therapeutic peanut butter-based food (‘chiponde’) a day. This ‘chiponde’ is rich in both energy and proteins and contains per 100 gram: 540 kcal, carbohydrates 27 grams, protein 13.6 gram, fat 35.7 gram. Vitamin A 910 μg, vitamin E 20 mg, zinc 14 mg, magnesium 92 mg [19]. We did not document the intake of chiponde or other food.
Patients were escorted home after the first post operative chemotherapy course. On the compound where they lived, the nutritional status of siblings, cousins and neighbours was assessed if permission was given to do so. These were used as healthy controls. Controls were included if their age was between one and 10 years and if both their parents were alive and healthy.

Statistical analyses were performed with SPSS (SPSS for Windows, version 16.0, SPSS, Chicago, Illinois). Pearson’s correlation coefficient was calculated to analyze correlation between different factors. P-values < 0.05 were considered significant.

Results

Patient characteristics
Twenty patients were studied, including 8 girls and 12 boys. Median age of the patients at diagnosis was 3 years and 10 months (range 12 months – 8.5 years). No patients were found to be HIV infected. Average duration of symptoms was 2 ½ months (range 1 month – 4 months). Eleven patients had a localized renal tumour, 8 had metastases, and 1 had bilateral renal disease. Average estimated tumour volume by ultrasound at diagnosis was 2.5 L (range 0.5 – 8.2 L).

Two patients abandoned therapy, one before any chemotherapy was given, another before surgery. Six patients received preoperative chemotherapy but were not operated upon; 1 died unexpectedly during induction of anaesthesia, five were considered inoperable with no other feasible curative treatment options (one primary tumour, 4 with metastases) [20].

Three patients had stable disease with a tumour decreasing < 25 % in size with preoperative chemotherapy, one patient had progressive disease, with a tumour increasing > 25 % in size. All other evaluable patients (14) had a partial response (>25 % decrease in size).

Community controls
Eighty three children were included as community controls to compare their nutritional status with the nutritional status of the patients. They were 43 (52%) girls and 40 (48 %) boys. The median age of these community controls was 3 years and 10 months (range 1.1 – 9.4 years).

Nutritional status of patients at diagnosis compared to community controls
At diagnosis mean (corrected) weight of patients was 12.2 kg (range 8.3 – 19.5 kg) and mean height was 94.9 cm (range 72 – 132 cm). Stunting (short for age) is a sign of chronic malnutrition and is defined as a Z-score for height for age of ≤ -2.
A similar percentage of patients and community controls was found to be stunted (chronically malnourished); 40% of patients and 37% of community controls (Table I). *Wasting* is a sign of acute malnutrition and is defined as a Z-score for weight for height of \( \leq 2 \). In our patients we used a *corrected weight*, because of the large tumour masses; corrected weight was defined as body weight minus tumour weight. Using this parameter we found 45% of our patients to be wasted (acutely malnourished), compared to only 11% of the community controls (Table I). Another parameter of acute malnutrition (independent of tumour mass) is an arm muscle area below the 5th percentile for age. Using this parameter, 55% of our patients were found to be acutely malnourished, compared to only 11% of community controls (Table I).

**Table I.** Nutritional status of patients at diagnosis and of community controls.

<table>
<thead>
<tr>
<th></th>
<th>Patients (N=20)</th>
<th>Community controls (N=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic malnutrition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Z-score height for age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>-1.6 (-3.9 - +0.5)</td>
<td>-1.6 (-4.9 - +3.6)</td>
</tr>
<tr>
<td>Z &lt; -2 (N/total N (%))</td>
<td>8/20 (40%)</td>
<td>31/83 (37%)</td>
</tr>
<tr>
<td><strong>Acute malnutrition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Z-score weight for height(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>-2.2 (-5.7 - -0.1)</td>
<td>-0.4 (-4.5 - +2.5)</td>
</tr>
<tr>
<td>Z &lt; -2 N/total N (%)</td>
<td>9/20 (45%)</td>
<td>9/83 (11%)</td>
</tr>
<tr>
<td>Arm muscle area</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>1052 (509 – 1589)</td>
<td>1354 (987 – 1989)</td>
</tr>
<tr>
<td>&lt; P5(^2) N/total N (%)</td>
<td>11/20 (55%)</td>
<td>9/83 (11%)</td>
</tr>
</tbody>
</table>

\(^1\) For patients Z-score for corrected weight for height is used (corrected weight = body weight minus tumour weight); \(^2\) \( < P5 = < \) the 5th percentile for age.

In conclusion, a large proportion of both patients and community controls had signs of chronic malnutrition. Acute malnutrition was common in patients with a Wilms tumour and less common in community controls. This suggests that the malignant disease plays a role in the development of acute malnutrition. In accordance with this we found that the degree of acute malnutrition at diagnosis was strongly correlated with the size of the tumour at diagnosis (\( r = -0.88, P < 0.01 \), Figure 1). The children admitted with larger tumours had more severe acute malnutrition.

**Serum levels of micronutrients at diagnosis**

We wanted to assess the prevalence of micronutrient deficiencies in this patient group with a high rate of both acute and chronic malnutrition. Surprisingly, serum
levels indicative of deficiency were rare, except for vitamin A. No patients had an abnormally low serum level of magnesium, and only one patient each of zinc and vitamin E. Forty four percent of patients (8/18) had an abnormally low level of retinol (vitamin A) of < 0.7 μmol/L.

**Change of nutritional status during preoperative chemotherapy.**

We aimed to evaluate in our patient group the effect of the nutritional intervention during preoperative chemotherapy with encouragement of oral feeds and supply of chiponde. This was done in the 18 patients who had completed preoperative chemotherapy. Mean corrected weight at diagnosis in this patient group (n=18) was 12.1 kg (SD 3.3, range 8.3 – 19.5) and was not significantly higher after 4 weeks of preoperative chemotherapy (12.5 kg (SD 3.0, range 8.0 – 21.4) (p =0.2). Mean percentage corrected weight gain was 5.8% (range -22 = 47). Within the whole group of patients, three subgroups could be defined. Seven patients had considerable (corrected) weight gain (>5%), 7 had a relatively stable (corrected) weight (< 5% change) and 4 had considerable (corrected) weight loss (>5%).

**Figure 1.** Correlation of Z-score weight for height (acute malnutrition) and tumour size at diagnosis. Pearson’s correlation coefficient (r) = -0.88 (P = < 0.01).

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Table II. Serum levels of micronutrients at diagnosis (N=18).

<table>
<thead>
<tr>
<th>Micronutrient</th>
<th>Mean (range)</th>
<th>Patients with abnormally low level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium (mmol/L)</td>
<td>0.88 (0.78 – 1.01)</td>
<td>0/18 (0%)</td>
</tr>
<tr>
<td>Zinc (μmol/L)</td>
<td>14.1 (9.7 – 23.5)</td>
<td>1/18 (6%)</td>
</tr>
<tr>
<td>Vitamin A (μmol/L)</td>
<td>0.83 (0.3 – 1.9)</td>
<td>8/18 (44%)</td>
</tr>
<tr>
<td>Vitamin E (μmol/L)</td>
<td>21.7 (3.4 – 46.7)</td>
<td>1/18 (6%)</td>
</tr>
</tbody>
</table>

Normal values: Magnesium 0.71 – 0.95 mmol/L; Zinc 11 – 24 μmol/L; Vitamin A 0.7 – 2.9 μmol/L; Vitamin E 8.8 – 42 μmol/L

In conclusion, 7 of 18 patients had considerable (corrected) weight gain during preoperative chemotherapy with our nutritional intervention.

Factors affecting change of nutritional status during preoperative chemotherapy

We considered tumour response to preoperative chemotherapy as a factor affecting nutritional change during preoperative chemotherapy. This correlation between change in nutritional status and tumour response to chemotherapy was clearly shown for the whole group of patients (r= 0.52, P < 0.05, Fig 2). Patients with a better response to preoperative chemotherapy had a more positive nutritional course. In accordance with this, the subgroup of 7 patients presented in the previous paragraph who all had a more than 5% weight gain during preoperative chemotherapy all had a > 40% tumour response to preoperative chemotherapy.

Anorexia

We also considered anorexia as a factor affecting the change in nutritional status during preoperative chemotherapy. We compared the group of patients with a maximum toxicity score for anorexia ≥ 2 with the group of patients who had an anorexia score < 2. In the group of patients with less severe anorexia (N=7), the mean (corrected) weight gain was higher at 9.0 % than in the group with more severe anorexia (N=10) at 3.4% (P=0.06). Not surprisingly, a higher percentage of children in the group treated with the 3 drug more intense regimen for metastatic disease had more severe anorexia; 8 of the 10 children with an anorexia score ≥ 2 were treated with the 3 drug regimen and all children (N=7) with an anorexia score < 2 were treated with the 2 drug regimen.
Discussion

This study evaluated the nutritional status of patients with a Wilms tumour in Malawi at diagnosis and during treatment. Anthropometry shows that about half of these patients are acutely malnourished at diagnosis. This is higher than the rate of 35% found by Wessels et al in South Africa, where the true incidence may have been underestimated by the weight of large tumours masking reduction of body weight [6].

This high rate of acute malnutrition is likely to be caused by a combination of chronic undernutrition at home and the presence of advanced disease in patients who presented after an average period of symptoms of 2.5 months. Of the community controls, 37% were stunted (= height for age < -2 SD), indicating chronic malnutrition; a percentage similar to that found in the patients (40%) and also similar to figures (45%) found by the United Nations’ International Children’s Fund (UNICEF) in a survey of Malawian children [4]. The patients, though, were more

![Figure 2. Correlation between response of the tumour (% decrease in size) and change in corrected weight (%) during preoperative chemotherapy. Pearson’s correlation coefficient (r) = 0.52 (P = < 0.05).]
often acutely malnourished than the controls (about 50% of patients vs. about 10% of community controls). These figures support the theory that the cause of the high rate of acute malnutrition at diagnosis is a combination of undernutrition (food shortage) at home and a delayed presentation with a large tumour load. This association between acute malnutrition and tumour load was also supported by the strong correlation found in our patients between degree of acute malnutrition and tumour size at diagnosis.

Forty four percent of patients were found to be vitamin A deficient at diagnosis. This is comparable to the rate of 53% found in healthy community control patients aged 6 – 60 months in a study by Calis et al in Malawi [21]. Vitamin A maintains the integrity of the epithelium in the respiratory and in the gastrointestinal tracts. Vitamin A deficiency increases the susceptibility of infection and overall mortality [13]. In Malawi, a national vitamin A supplementation programme is in place for all children between 6 – 59 months of age [4]. Full coverage is reported to be reached for 86% of children, and at least one dose is given to 94% of all children [4].

Dietary sources of vitamin A in Malawi are carrots (not freely available and mango (widely available in the hot/wet season). We may need to consider to supplement vitamin A to all children admitted with cancer.

Only one child was found to be zinc deficient. Malawi is known to be a high risk area for zinc deficiency, with a high prevalence of stunting (one of the symptoms of zinc deficiency) [13]. Maize, which is the staple diet in Malawi, has a high phytate concentration which limits bioavailability of zinc [22]. Plasma zinc concentration is the most widely accepted biomarker of zinc status, but has a known low sensitivity [22]. This may be part of the explanation why surprisingly few of our patients had an abnormally low serum zinc level.

Locally made peanut butter based ready-to-use-therapeutic food (RUTF) is an attractive way to give nutritional support in the Malawian setting. It is an energy and protein rich mix supplemented with minerals and micronutrients and is increasingly widely used in the treatment of malnourished children in developing countries [23]. It does not need to be mixed with water or cooked and has a long shelf life. Most children love the sweet taste and sticky texture [24,25].

It is difficult to draw conclusions from the results of changes of nutritional status during preoperative chemotherapy in our patients. Patient numbers are small and differences in mean corrected weight before – and after preoperative chemotherapy not statistically significantly different. Still, it is encouraging that with the supply of chiponde 7 children had a more than 5% (corrected) weight gain after 4 weeks of preoperative chemotherapy. Not surprisingly, the change in corrected weight was correlated with the tumour response to preoperative chemotherapy. The efficacy of nutritional support with chiponde in children with cancer in resource limited countries needs further study.
We did not document the total daily intake of calories, chiponde or other food, since this is not feasible in our setting. We encouraged patients and guardians, on an almost daily basis, to finish one jar of chiponde a day which is 245 gram (1320 kcal). It has been described in resource rich settings that nutritional support either with parenteral nutrition or via a gastric tube can improve nutritional status of patients with Wilms tumour during therapy [26,27]. Different protocols and guidelines exist as to when to start this type of nutritional support [28]. An algorithm developed in the St Jude Children’s research hospital uses the following criteria to start nutritional support: weight loss > 8 % or weight < 90 % of ideal body weight or albumen < 35 mmol/L [29]. On the basis of weight corrected for estimated tumour weight; 17 of our 20 patients would qualify according to these criteria for nutritional support, since this weight would be < 90 % of their ideal body weight. There are several reasons why nasogastric tube feeding is infrequently used in children with cancer in Malawi. Firstly, the malnutrition is caused in part simply by food shortage at home. Secondly, nursing care is strained by lack of human resources and lastly, parental acceptance of nasogastric tubes is low, especially when children can eat. The advantages of gastric tube feeding then have to be weighed against the risk of treatment abandonment. Early presentation will probably be the most effective way to improve the nutritional status of patients with a Wilms tumour at diagnosis. Encouraging oral feeds and supply of sufficient energy and protein rich foods to malnourished patients
is essential, but sometimes not enough to restore nutritional status. The efficacy of nutritional support with chiponde in children with cancer in resource limited countries needs further study. NGT nutritional support may need to be considered, especially in a subgroup of severely malnourished and anorectic patients.

Patient (3 years old) with a Wilms tumour and obvious wasting (acute malnutrition).

Height measuring of the ‘community controls’ during the home visit.
Literature


4. UNICEF. The state of the world’s children. 2006.


