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Artículo de revisión

Assessing the impact of nutritional status on clinical outcomes in children and adolescents with cancer: A focus on the contributions from Mexico

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RESUMEN

El estado nutricional de los niños con cáncer es importante y con frecuencia afecta a la enfermedad misma y a su tratamiento; se relaciona con el estado socioeconómico de los pacientes. Algunos investigadores mexicanos han tendido un papel prominente en los úiltimos 20 años, explorando la reacción entre la deficiencia del estado nutricional y la esperanza de vida de los pacientes. Los mecanismos que explican estas observaciones no se conocen por completo y han creado oportunidades de afectuar un estudio en el país orientado a explorar y aclarar esta asociación, así como a hacer intervenciones terapéuticas para mejorar los resultados del tratamiento de estos pacientes. Este tipo de estudios podría consolidar la tradición de la investigación en aspectos nutricionales que se ha efectuado en México desde hace muchos años. Como parte de las actividades orientadas a continuar con estas investigaciones, en la ciudad de Puebla se realizaron, en los años de 1997 y 2006, unos talleres que debieran constituirse en el fundamento del futuro de estas investigaciones.
Palabras clave: nutrición, cáncer, niños, resultados terapéuticos.

SUMMARY

The nutritional status of children with cancer is clinically important and often compromised by the malignant disease and its treatment as well as pre-existing socio-economic disadvantage. Investigators in Mexico have played a prominent role over the past 20 years in exploring the relationship between diminished nutritional status and reduced prospects for survival. Mechanisms underlying this association remain incompletely resolved, but clear opportunities exist to undertake a national initiative in Mexico focused on this challenge and the related target of devising effective nutritional interventions to improve clinical outcomes. Such undertakings would consolidate the position of clinical nutritional research in Mexico within the vanguard of this scientific enterprise in pediatric oncology. This leadership is exemplified by the two international workshops on the topic convened in Puebla in 1997 and 2006, providing a firm foundation for further progress.
Key words: nutrition; cancer; children and outcomes.

For the purposes of cancer registration, children with malignant neoplasms are defined by international convention as being 0-14 years of age and a widely accepted classification system for these diseases in this age group is in common use.[1] Likewise, there is increasing acceptance that adolescents with cancer occupy the age range 15-19 years,[2] although a uniform system for classifying the malignant diseases in this age group is still in evolution.[3]

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It is a harsh reality that the great majority of children and adolescents live in low income countries (LIC),[4] in the poorest of which the gross national income per capita is less than US $1000 per year, compared to almost US $40,000 in industrialized societies.[5] Although the incidence rate of cancer in childhood in LIC is less certain than in Western Europe and North America,[6] and the rate in adolescents in LIC is entirely unknown, it is clear that the great majority of cases occur in disadvantaged societies.[7]

NUTRITION IN CHILDREN

It goes almost without saying that adequate nutrition is essential to normal growth, development and well-being throughout childhood and adolescence. Perturbations of nutritient intake may result in under-nutrition (commonly described as malnutrition) or over-nutrition (leading to being overweight and obesity). The former is more prevalent in

LIC and the latter in industrialized societies, though both are recognized in both settings (as described in a contribution from Mexico),[8] and both are associated with compromised clinical outcomes in children with cancer (see below). Given the focus of this review and the circumstances in LIC, the following discussion will emphasize the importance of malnutrition in young people with cancer, and highlight the contributions to our understanding of the relationship by clinical investigators in Mexico.

The World Health Organization (WHO) defines acute malnutrition as wasting, on the basis of the index weight-for-height (WFH), and chronic malnutrition as stunting, on the basis of the index height-for-age.[9] There are limitations to the use of these WHO criteria, especially in children and adolescents with cancer. Like the corresponding WFH index from the Centres for Disease Control and Prevention (CDC)[10] in the United States, the WHO index is applicable only to children less than 6 years of age. Furthermore, WFH may underestimate acute malnutrition in the presence of solid tumor that may account for more than 10% of body weight.[11] Alternative measures of body composition that are independent of weight include triceps skin fold thickness (TSFT) and mid-upper arm circumference (MUAC). TSFT correlates well with fat mass and MUAC with lean body mass in newly diagnosed children with cancer,[12] as well as in healthy children (Table 1), as these components are measured by dual energy X-ray absorptiometry (DXA scans).

The prevalence of malnutrition in children with cancer was described first in Mexico by Rivera-Luna et al at the National Institute of Pediatrics[13] and by Lobato-Mendizabal and colleagues in Puebla[14] more than 20 years ago in patients with non-Hodgkin lymphoma (NHL) and acute lymphoblastic leukemia (ALL) respectively. More than 1/3 of them were undernourished on the basis of weight-for-age and gender. It was appropriate then that the first international workshop on this topic was held in Mexico in November 1997, with the proceedings published as a supplement to the International Journal of Cancer under the title 'Nutritional Morbidity in Children with Cancer – Mechanisms, Measures and Management.[15] In 2002 Sosa-Ruiz and colleagues in Mexico City reported that the frequency of malnutrition at diagnosis in children with solid tumours was more than twice as high (>50%) when determined by arm anthropometry (TSFT and MUAC) than by WFH (<25%).[16]

Table 1. Body Composition in Healthy Children and Adolescents. Comparisons of Skin Fold Measurements with DXA[a]

First Author	*Study Site*	*Number of Subjects*	*Age Range (years)*
Gutin	USA	43	9-11
De Lorenzo	ITALY	26	15.5 – 18[b]
Dezenberg	USA	202	4 – 11
Treuth	USA	101	8 – 9[c]
Eisenmann	USA	75	3 – 8
Rodriguez	SPAIN	238	13 – 18
Chomtho	UK	110	4.5-14

a = Dual Energy X-ray Absorptiometry, b = Males only; c = Females only.

SOCIO-ECONOMIC STATUS

It did not take long for recognition to come that malnutrition in children and adolescents with cancer was all-too-often part of a broader spectrum of social disadvantage, linked closely to poverty. Again it fell to the group in Puebla to be among the first to report the association.[17] Viana and colleagues in Belo Horizonte, Brazil provided corroboration[18] as did investigators in Monterrey.[19]

RELATIONSHIP OF NUTRITIONAL STATUS TO CLINICAL OUTCOMES

While obesity has been shown in North America to have an adverse impact on outcomes in children with ALL[20] and acute myeloid leukemia,[21] the focus in LIC has been on the deleterious effect of malnutrition. In their original report Lobato-Mendizabal et al observed a much lower 5 year survival rate in malnourished children and adolescents with ALL (26%) compared to adequately nourished patients (83%),[13] a pattern reported by most but not all investigators[22] since. Two groups from Mexico City[23, 24] have reported that death during remission induction is commoner in malnourished children, while Rivera-Luna et al reported that 6 of 7 severely malnourished children with NHL died during treatment.[13]

Again the group in Puebla recognized the striking association between poverty and compromised survival in children with ALL.[17] This association escaped the authors of studies in the United Kingdom[25, 26] addressing the effect of nutritional status on outcome in children and adolescents

with ALL, although it was suggested subsequently[27] that poverty was the fundamental link. But what is or are the mechanism(s)?

The investigators in Puebla pointed to reduced tolerance of chemotherapy in malnourished children[28, 29] This prompted a collaborative study with colleagues in Monterrey[19] to assess the influence of a simple dietary intervention. While the conclusion, that a fortified snack improved both nutritional status and hematological tolerance, may be subject to challenge on the basis of methodology, it remains the only report, of which this author is aware, of the implementation of such a therapeutic strategy.

The "Scottish conundrum"[27] suggested an additional mechanism to explain the association between malnutrition, poverty and poor outcome in children and adolescents with ALL; namely, reduced compliance with oral chemotherapy. Soon thereafter Viana and colleagues reported such an association in Brazilian children.[30] At its most extreme, non-compliance is manifest as abandonment of treatment, a phenomenon that has been described as the commonest course of treatment failure in children with cancer in Central America.[31] The high prevalence of abandonment is modifiable with the provision of social supports.[32] Poor nutritional status has been correlated with abandonment of therapy, the risk of relapse and a lower prospect of survival in children and adolescents with cancer in LIC.[33]

Figure 1. Participants at the first and second international workshop on nutrition in children with cancer

CONTINUING PROGRESS

A second international workshop on nutritional cancer in children was held in Puebla in November 2006.[34] This was attended by invited participants from 10 countries (Figure 1) and included a review of their experience by investigators from Monterrey.

Jamie-Perez and colleagues reported on studies of nutritional status in more than 100 patients with ALL.[35] In addition to a food frequency questionnaire, measurements were made of body mass index (BMI), TSFT, MUAC and body composition by DXA scan. By BMI 12% of the patients were under-nourished and this proportion exceeded 20% by DXA, though no details were provided. The results of arm anthropometry were said to be normal but no results were shown. This experience indicates that comprehensive studies of nutritional status in children with cancer in Mexico are not only possible but clinically informative and may be complemented by sophisticated techniques in selected circumstances.[36]

OPPORTUNITIES AHEAD

Notable exceptions notwithstanding, it appears that malnutrition at diagnosis can be an adverse prognostic factor in children and adolescents with the commonest form of cancer in this age group – ALL.[37] This may be true both for early treatment related mortality and for long term survival. It is likely that the mechanisms are different in these two circumstances, demanding further study.

Given the marked increases in the number of children diagnosed with ALL in Mexico[38] (likely a reporting bias); the level of interest among several groups of investigators about the importance of nutritional status in this context; and the demonstrated ability of these clinicians and

others to undertake the requisite measurements, there is a clear opportunity for collaborative studies in this area. In particular, a national initiative may be possible with appropriate co-ordination, as has been accomplished by the Asociación Hematologia-Oncologia Pediatrica de Centro-America.[39] Such an initiative could accrue sufficiently large numbers of subjects to provide the statistical power to address several important variables while affording the opportunity to undertake studies of nutritional interventions that are long-overdue and that Mexico is well-positioned to conduct.

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