Original Article

HPV-induced recurrent laryngeal papillomatosis: dietary fatty acid and micronutrient intakes

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Human papilloma virus (HPV)-induced recurrent laryngeal papillomatosis (RLP) is a chronic debilitating disease often encountered among children of poor socio-economic South African groups. There are a few studies and limited evidence as to what extent nutrition may contribute to this disease. To our knowledge this is the first study that gives an account of dietary FA and micronutrient intakes in RLP patients, according to food frequency questionnaires. The dietary FA profile revealed an excessive linoleic acid (LA) intake syndrome and is also marked by high palmitic acid (PA), oleic acid (OA) and SFA intakes. Research revealed that enhanced LA and PA drive, respectively, mitogenetic stimuli and apoptotic resistance during tumorigenesis, whist SFAs are associated with lipid rafts, the Th1 immune response and immunosuppression. Low folate intake, a risk for HPV-infection, and low Zn intake, detrimental for lipid metabolism and immunocompetence, occurred in, respectively, 70 % and 20% RLP patients. The poor correlations that were found in RLP patients between essential fatty acids (EFAs) and micronutrients, namely, Mg, Zn and Se, involved in lipid metabolism and immune responses, need proper clarification. Overall, it is plausible that the diet (poor nutrition), a shift in lipid metabolism caused by HPV- infection, environmental smoke and oxidative stress, as well as extra-esophageal acid reflux with secondary inflammation in the larynx are co-factors in the etiology of laryngeal papillomatosis, and that immunocomprised patients are subjected to recurrence. It is imperative to ensure that children with RLP receive proper nutrition and follow a healthy lifestyle to prevent disease recurrence after treatment.

Key Words: Papillomatosis, fatty acids, micronutrients, immunodeficiency, immunonutrition

INTRODUCTION

Urgent strategies are required to combat human papilloma virus (HPV)-induced recurrent laryngeal papillomatosis (RLP) among poor socio-economic groups in developing countries. Malnutrition and inadequate diets among poor socio-economic groups in South Africa usually contribute to immunocompromised individuals and especially HPV-infected children are subjected to RLP. Obstruction of the airway is a life-threatening sign and the mainstay treatment is surgery until the disease regresses spontaneously. Despite several adjuvant treatment modalities with anti-viral drugs, current management of RLP is palliative at best. There is still an ongoing search for appropriate vaccine(s) to prevent or combat laryngeal papillomatosis. A nutritional disadvantage in children with RLP may definitely hamper current treatments and influence the clinical course of the disease. Therefore, it is imperative to improve the immunocompetence of RLP patients.[1-5] Dietary intakes that do not meet with daily recommendations may be a predicament and it is commonly known that the Western diet with an excessive linoleic acid (LA) intake syndrome can contribute to inflammatory conditions and diseases.[6-8] There are a few studies and limited evidence as to what extent nutrition may contribute to this RLP.

The main goal of our comprehensive lipid study was to establish a FA profile for RLP tumors, already reported,[9] and dietary FA intake and micronutrient profiles for RPL patients, presented in this paper, to identify FA and micronutrient role-players that can contribute to tumorigenesis and immunosuppression in these patients. In an attempt to assess whether the diet may be a co-factor in the etiology of RLP, it is necessary to address factors that can interfere with lipid metabolism. Of relevance to this study is that viruses and saturated fatty acids (SFAs) may interfere with essential fatty acid metabolism (EFAM) by impeding delta-6 and -5 desaturase (Δ6 and Δ5) activities and the conversion of LA (substrate for the n-6 FA pathway) and α-linolenic acid (α-LA) (substrate for the n-3 FA pathway) to their important biological metabolites, with essential fatty acid deficiency (EFAD) as a consequence.[9] This phenomenon is marked by a shift in lipid metabolism, whereby, the n-7 and n-9 FA pathways are followed with enhanced de novo fatty acid synthase (FAS) and Δ^9d activities and the production of palmitic acid (PA), stearic acid (SA) and OA, associated with tumorigenesis and immunosuppression.[9,10-15] The FA profile of RLP tumors confirmed such a shift in lipid metabolism and identified LA and SFAs as role-players that contribute to RLP.[9] The question that remained was how do

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dietary FAs contribute to the papilloma FA profile? Of further relevance to this study is that zinc (Zn) and magnesium (Mg) are considered necessary co-factors for normal Δ^6d activities, and that selenium (Se) and Zn have significant effects on the immune system.[16,17] The question was raised whether these micronutrient intakes in RLP patients were sufficient. These questions prompted the construction of FA and micronutrient profiles and a correlation study between micronutrients and FAs was also performed.

SUBJECTS AND METHODS

To assess the diets of the RLP patients in our study group (n10), eight patients (n8) (between 4 and 10 years), together with their matching controls (tonsillectomy patients) (n8), were selected to confer to a more appropriate age group for comparative purposes. Food frequency questionnaires (FFQs) were completed by questioning the parents or guardians of the RLP and tonsillectomy patients. Food portion sizes were estimated in household measures and milliliters and converted to grams, using the Food Quantities Manual.[18] The dietary data were analyzed, using MRC Food Composition Tables.[19] The median FA intakes were compared with recommended dietary allowances (RDAs) and micronutrient intakes were compared with dietary reference intakes (DRIs), to enable comparison of the results of this study with those of other studies.[20, 21]

Descriptive statistics, namely frequencies and percentages for categorical data and means and medians for continuous data, were calculated per group. To compare groups within the same patient statistically, the paired student-*t* test and signed rank test for parametric or non-parametric data were used and 95% confidence intervals (95% CI) for the mean or median differences were calculated. In the case of comparison between patients and controls the student t-test and Mann-Whitney test were performed. Spearman correlations and *p*-values were used for comparisons between micronutrients and fatty acids.

RESULTS

FFQs confirmed a typical Western diet with excessive LA intake for both the RLP patients (tumor group) and tonsillectomy patients (control group). The diets of RLP patients compared with tonsillectomy patients showed more or less similar energy intakes (6309 kJ vs. 7116 kJ) and macronutrient intakes: proteins (44.8g vs. 55.0g); carbohydrates (160g vs. 176g) and total fat (67.6g vs. 66.2g). Both patient groups came from the same poor socio-economic community and small differences may be attributed to slightly poorer appetites among the RLP children. In the case of RLP patients, an excessive dietary LA intake (21.1 g/d, compared with a recommendation of 7-11 g/d) and an adequate intake of n-3 PUFAs (1.47 g/d, compared with a recommendation of 1- 1, 5 g/d) occurred.[20] Other major dietary FA intakes (values expressed as means and standard deviations) are as follow: PA (19.8± 3.32) and OA (42.9±3.72). In the case of tonsillectomy patients, an excessive dietary LA intake (22.1 g/d, compared with a recommendation of 7-11 g/d), and an adequate intake of n-3 PUFAs (1.74 g/d, compared with a recommendation of 1- 1, 5 g/d) occurred.[20] Other major dietary FA intakes were: PA (20.3±1.24) and OA (39.7±2.15). When FA groups within each patient group were compared, the SFA intake was significantly higher in all the cases. Values of relevance to this study are summarized as follow: SFA intakes compared with unsaturated fatty acid (UFA) intakes in RLP patients ($p<$ 0.008; CI for median of differences [10.1;28.9]), SFA intakes compared with MUFA intakes in RLP patients ($p<$ 0.008); CI for median of differences[0.63;14.8]); SFA intakes compared with UFA intakes in tonsillectomy patients ($p<$ 0.008; CI for median of differences [9.02;23.9]); SFA intakes compared with MUFA intakes in tonsillectomy patients ($p<$ 0.008; CI for median of differences[0.68;7.59]). Apart from the above major FA role-players, the presence of arachidonic acid (AA) in the diets of RLP and tonsillectomy patients needs to be mentioned. Although exogenous AA intakes were low, respectively, (0.05± 0.02) and (0.04±0.02) in RLP and tonsillectomy patients, metabolic conversion in the case of RLP patients is inhibit by the HPV and it serves as an additional source for oxidative stress and inflammation.[22,23] In the case of tonsillectomy patients, exogenous intake and endogenous production of AA contributes to the characteristic inflammatory condition encountered.

Micronutrient intakes of RLP and tonsillectomy patients are summarized in Table 1. Low micronutrient intakes with a high incidence among the RLP patients were Vitamin D (7 patients ≤ 67% RDA) and folate (7 patients ≤ 67% RDA). Of significance is that folate deficiency is associated with a high HPV risk.[24] Zn and Se deficiencies observed in some RLP patients deserve further attention, since they may play prominent roles in the immunocompetence of the patients. Interestingly, the same high incidence of low folate intake was also observed in the tonsillectomy patients (7 patients ≤ 67% RDA). This may imply that tonsillectomy patients have a high risk for HPV-infection. Although the incidence of HPV-infection in tonsillectomy patients is low (2%), the possibility of infection among individual tonsillectomy patients in this study can not be outruled.[25]

Mostly poor correlations between micronutrient intakes and individual FAs in the diets of RLP patients occurred, with a few exceptions (see Table 2). Poor correlations were found when Mg, Zn, Se and riboflavin were compared with LA (18:2n-6), AA (20:4n-6), α-linolenic acid (α-LA) (18:3n-3), eicosapentaenoic acid (EPA) (20:5n-3) and docosahexaenoic acid (DHA) (22:5n-3) , whilst good correlations occurred between palmitoleic acid (PLA) and Zn (r 0.64; p <0.08), PLA and Se (r 0.76; p < 0.02) and SA and riboflavin (r 0.78; p < 0.02). Among tonsillectomy patients, mostly good correlations between micronutrients and EFAs occurred, with the exception of LA (see Table 3). These correlations may be related to the types of foods eaten by the children. It is possible that where good correlations were seen these are due to the nutrients occurring in common food sources, while poor correlations may reflect the low fat content in most foods high in Mg, Zn, Se and riboflavin. The good correlations observed between micronutrients and individual FAs may imply the body's attempt to fight the virus infection and oxidative stress, whilst the poor correlations apparently

emphasize excessive or inadequate EFA intakes in the diets of RLP and tonsillectomy patients. These assumptions need to be confirmed or refuted.

Table 1. Micronutrient intakes in recurrent laryngeal papillomatosis (tumor) and tonsillectomy (control) patients.

MICRO-NUTIENTS	MEDIAN	RDA /AI	RDA / AI (≤67%)	RDA / A1 (≥67%)
Ca (Tumor)	811	800mg	2	6
Ca (Control)	823	800mg	2	6
Cu (Tumor)	0.84	1.5mg	0	8
Cu (Control)	1.20	1.5mg	0	8
Fe (Tumor)	9.78	8mg	2	6
Fe (Control)	15.4	18mg	1	7
Fol (Tumor)	136	200µg	7	1
Fol (Control)	145	200µg	7	1
Mg (Tumor)	227	130mg	0	8
Mg (Control)	268	130mg	0	8
RA (Tumor)	685	400µg	1	7
RA (Control)	1027	400µg	0	8
Se (Tumor)	28.9	30µg	2	6
Se (Control)	42.6	30µg	1	7
V_{B1} (Tumor)	0.60	0.6mg	1	7
V_{B1} (Control)	0.88	0.6mg	2	6
V_{B2} (Tumor)	1.10	1.2µg	1	7
V_{B2} (Control)	1.49	1.2µg	0	8
V_C (Tumor)	137	25mg	0	8
V_C (Control)	225	25mg	0	8
V_D (Tumor)	2.97	5µg	5	3
V_D (Control)	1.59	5µg	6	2
Zn (Tumor)	6.07	5mg	2	6
Zn (Control)	7.94	5mg	2	6

Abbreviations: AI: adequate intake; RDA: recommended dietary allowance.
Micronutrients: Ca: calcium; Cu: copper; Fe: iron; Fol: folate; Mg: magnesium; RA: retinoic acid; Se: selenium; V_{B1}: vitamim $_{B1}$ (thiamine); V_{B2}: vitamin $_{B2}$ (riboflavine); V_C: vitamin C; V_D: vitamin D; Zn: zinc

Table 2. Correlation between micronutrient and fatty intakes in the diets of tumor patients.

MICRO-NUTRIENTS	FATTY ACIDS						
	PLA	**SA**	**LA**	**AA**	**α-LA**	**EPA**	**DHA**
Ca (r-value)	-0.59	-0.02	0.07	-0.21	0.73	-0.59	-0.73
Ca (*p*-value)	0.11	0.95	0.86	0.61	0.03	0.11	0.3
Cu (r-value)	0.52	0.28	-0.33	0.73	0.33	0.11	0.42
Cu (*p*-value)	0.18	0.49	0.41	0.03	0.41	0.77	0.28
Fe (r-value)	0.14	0.40	0.40	0.54	-0.21	-0.14	-0.23
Fe (*p*-value)	0.73	0.31	0.31	0.03	0.73	0.73	0.57
Fol(r-value)	0.54	0.14	0.21	-0.02	0.35	0.64	0.40
Fol (*p*-value)	0.16	0.73	0.61	0.95	0.38	0.08	0.31
Mg (r-value	0.16	0.30	0.14	0.47	-0.21	-0.16	-0.19
Mg (*p*-value)	0.69	0.45	0.73	0.23	0.61	0.69	0.65
RA (r-value)	0.47	0.42	0.38	-0.07	0.83	0.52	0.61
RA (*p*-value)	0.20	0.28	0.35	0.86	0.01	0.18	1.10
Se (r-value)	0.76	0.47	0.40	0.45	0.59	0.23	0.33
Se (*p*-value)	0.02	0.23	0.31	0.26	0.11	0.57	0.41
V_{B1} (r-value)	0.61	0.80	0.50	-0.16	0.26	0.09	-0.09
V_{B1} (*p*-value)	0.10	0.01	0.20	0.69	0.53	0.82	-0.82
V_{B2} (r-value)	0.52	0.78	-0.23	0.11	0.23	-0.09	0.07
V_{B2} (*p*-value)	0.18	0.02	0.57	0.77	0.57	0.08	0.86
V_C (r-value)	0.61	0.47	-0.11	-0.33	0.54	0.54	0.47
V_C (*p*-value)	0.10	0.23	0.77	0.41	0.16	0.16	0.23
V_D (r-value)	0.54	0.33	0.78	-0.33	0.64	0.61	0.35
V_D (*p*-value)	0.16	0.41	0.02	0.42	0.08	0.10	0.38
Zn (r-value)	0.64	0.54	0.30	0.54	0.40	0.02	0.16
Zn (*p*-value)	0.08	0.16	0.45	0.16	0.31	0.95	0.69

Abbreviations: r-value: correlation between micronutrient and fatty acid; *p*-value: significance/non-significance between micronutrient and fatty acid.
Fatty acids: PLA: palmitoleic acid (16:1); SA: stearic acid (18:0); LA: linoleic acid (18:2n-6); αLA: α-linolenic acid (183n-6); AA: arachidonic acid (20:4n-6); EPA: eicosapentaenoic acid (20:5n-3); DHA: docosahexaenoic acid (22:5n-3).
Micronutrients: Ca: calcium; Cu: copper; Fe: iron; Fol: folate; Mg: magnesium; RA: retinoic acid; Se: selenium; V_{B1}: vitamim $_{B1}$ (thiamine); V_{B2}: vitamin $_{B2}$ (riboflavine); V_C: vitamin C;V_D:vitamin D; Zn: zinc

Table 3. Correlation between micronutrient and fatty acid intakes in the diets of control patients.

MICRO-NUTRIENTS	FATTY ACIDS						
	PA	**SA**	**LA**	**α-LA**	**AA**	**EPA**	**DHA**
Ca (r-value)	0.26	0.33	0.54	0.90	0.76	0.57	0.47
Ca (*p*-value)	0.53	0.41	0.16	0.00	0.02	0.13	0.23
Cu (r-value)	0.11	0.14	0.47	0.83	0.57	0.40	0.28
Cu (*p*-value)	0.77	0.73	0.23	0.01	0.13	0.31	0.49
Fe (r-value)	0.21	0.30	0.54	0.83	0.57	0.59	0.57
Fe (*p*-value)	0.61	0.45	0.16	0.01	0.13	0.07	0.13
Fol (r-value)	0.23	0.26	0.42	0.73	0.83	0.57	0.38
Fol (*p*-value)	0.57	0.53	0.28	0.03	0.01	0.13	0.35
Mg (r-value)	0.35	0.40	0.64	0.90	0.71	0.66	0.54
Mg (*p*-value)	0.38	0.31	0.08	0.002	0.04	0.07	0.16
RA (r-value)	0.23	0.38	0.09	0.47	0.50	0.35	0.61
RA (*p*-value)	0.57	0.35	0.82	0.23	0.20	0.38	0.10
Se (r-value)	0.28	0.57	0.14	0.38	0.50	0.73	0.95
Se (*p*-value)	0.49	0.13	0.73	0.35	0.21	0.03	0.03
V_{B1} (r-value)	0.11	0.07	0.38	0.38	0.61	0.19	0.00
V_{B1} (*p*-value)	0.77	0.86	0.35	0.35	0.10	0.65	1.00
V_{B2} (r-value)	0.35	0.28	0.54	0.64	0.83	0.42	0.21
V_{B2} (*p*-value)	0.38	0.49	0.16	0.08	0.01	0.28	0.61
V_C (r-value)	0.07	0.23	0.16	-0.09	0.21	0.16	0.00
V_C (*p*-value)	0.86	0.57	0.69	0.82	0.61	0.69	1.00
V_D (r-value)	0.57	0.64	0.71	0.95	0.88	0.69	0.54
V_D (*p*-value)	0.13	0.08	0.04	0.003	0.003	0.05	0.16
Zn (r-value)	0.09	0.26	0.28	0.76	0.76	0.47	0.45
Zn (*p*-value)	0.82	0.53	0.49	0.01	0.02	0.23	0.26

Abbreviations: r-value: correlation between micronutrient and fatty acid; *p*-value: significance/non-significance between micronutrient and fatty acid.
Fatty acids: PA: palmitoleic acid (16:1); SA: stearic acid (18:0); LA: linoleic acid (18:2n-6); α-LA: α-linolenic acid; (18:3n-3) AA: arachidonic acid (20:4n-6); EPA: eicosapentaenoic acid (20:5n-3); DHA: docosahexaenoic acid (22:5n-3)
Micronutrients: Ca: calcium; Cu: copper; Fe: iron; Fol: folate; Mg: magnesium; RA: retinoic acid; Se: selenium; V_{B1}: vitamim $_{B1}$ (thiamine); V_{B2}: vitamin $_{B2}$ (riboflavine); V_C: vitamin C; V_D: vitamin D; Zn: zinc

DISCUSSION

The dietary FA profile of RLP children revealed an excessive LA intake syndrome and is also marked by high PA, OA and SFA intakes. The excessive LA serves as a source for cell proliferation and oxidative stress during tumorigenesis, apart from conjugated linoleic acid (CLA) production that is not addresses in this paper.[26-28] When EFAM is impeded, FAS and Δ9d activities prevail, a situation often encountered in malnourished humans and inflammatory diseases. The main product of de novo FAS is PA and constant high PA levels (exogenous intake and endogenous production) can contribute to maintenance of cell proliferation, apoptotic resistance, oxidative stress and immune responses.[14,15,22,26,29,30] Enhanced OA (exogenous intake and endogenous production) is a hallmark of tumorigenesis.[14] Currently, there is renewed interest in the down-regulation of FAS and Δ9d activity by GLA.[31,32] Of significance is that FAS inhibition may mainly affect synthesis of raft-associated lipids, namely SFAs, and these lipid rafts are associated with Th1 down-regulation of the immune system.[10] Of further significance is that LA, AA and SFAs may contribute to cumulative oxidative stress and inflammation,[22] mechanisms that underlie RLP. It is postulated that papillomatosis begin at squamo-columnar epithelial junctions, an ideal microenvironment for HPVs to grow and thrive, and that environmental smoke (free radicals) and acid from an extra-esophageal acid reflux may accumulate here and contribute to oxidative stress and inflammation.[9] Moreover, angiogenesis that is characteristic of tumorigenesis allows constant circulation of excessive LA and PA to papilloma cells and they continue to proliferate and survive. Therefore, it is plausible that the diet is a co-factor in the etiology of these tumors.

There is tremendous interest in the modulatory effect of dietary lipids and phytochemicals on inflammatory and immune responses to improve immunocompetence for prevention of diseases, even in virally challenged patients.[33,34] The immunomodulatory potential of CLA and EPA is well established.[26,35] Among phytochemicals, indole-3 carbinol is a naturally occurring product of cruciferous vegetables (such as cabbage, cauliflower and broccoli) that is reported in the literature to be beneficial for the treatment of RLP, since it inhibits tumorigenesis.[36] A diet that prevents extra-oesophageal acid reflux and secondary inflammation underlying papillomatosis is strongly recommended in an attempt to prevent RLP.[37] Patients also need to be treated according to their individual micronutrient profiles. Of particular importance may be that Se is reported to increase interleukin-2 (IL-2) production and, thereby, improves anti-viral resistance.[17] In the case of Zn deficiency, research revealed that Zn supplementation can decrease cyclooxygenase-2 (COX-2) activity and oxidative stress and thereby, apart from preventing tumorigenesis, can increase maturation of lymphocytes to improve immune function.[16,38] The beneficial inclusion of Zn and / or folate supplementation in the therapeutic regime of RLP need to be properly evaluated.

From all the preceding information it is clear that malnutrition, activation of the HPV and a shift in lipid metabolism, environmental smoke and oxidative stress, as well as extra-esophageal acid reflux with secondary

inflammation in the larynx, may all be considered co-factors in the etiology of RLP. There is overwhelming evidence in the literature regarding the immunomodulatory potential of specific FA agents (CLA and EPA) and a rationale for adjuvant FA therapy in the management of RLP is proposed in another paper.[39]

CONLUSION

The findings of our comprehensive lipid study is in accordance with the viewpoint that in South Africa, among poor socio-economic communities where maize is the staple nutrition,[40] excessive LA and SFA intakes contribute to disease and immunodeficiency.[40] Overall, the FA profiles for RLP tumors, dietary FA intakes and micronutrient intakes support the viewpoint that the diet is a co-factor in the etiology of RLP. Therefore, it is imperative to ensure that children with RLP receive proper nutrition and follow a healthy lifestyle to prevent disease recurrence after treatment.

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AUTHOR DISCLOSURES

Louise Louw and Corina Walsh, no conflicts of interest.

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Original Article

HPV-induced recurrent laryngeal papillomatosis: dietary fatty acid and micronutrient intakes

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HPV 誘導喉頭乳瘤復發症：膳食脂肪酸及微量營養素攝取

人類乳突病毒誘發週期性的喉頭乳瘤(RLP)是一種慢性使人衰弱的疾病，好發於社經狀況較差的南非族群的兒童之間。僅有少數研究及有限的證據說明營養情況對此疾病的影響。就我們的認知，這是第一個研究，根據食物頻率問卷考慮 RLP 病人的膳食脂肪酸及微量營養素的攝取。膳食脂肪酸數據顯示過多的亞麻油酸(LA)攝取，棕櫚酸(PA)、油酸(OA)及飽和脂肪酸攝取也高。研究顯示較多的 LA 及 PA，在腫瘤新生期間會分別刺激細胞分裂及阻抗細胞凋亡；而飽和脂肪酸與脂質促進 Th1 免疫反應及免疫力之抑制有關。低葉酸攝取是 HPV 感染的危險因子，而低鋅攝取，不利於脂質代謝及免疫能力，這兩者分別發生在 70%和 20%的受測 RLP 病人中。另外發現在 RLP 病人，必須脂肪酸攝取與脂質代謝及免疫反應攸關的微量營養素，即鎂、鋅及硒的攝取量之相關性很小，這結果需要更進一步的釐清。整體來說，飲食(較差的營養)、HPV 感染引起的脂質代謝轉變、環境菸害、氧化壓力，以及因次級發炎引起的額外食道酸液回流，在喉頭乳瘤症的病因學是共因子，而免疫功能不全的病人較容易復發。因此，確定 RLP 的兒童在治療之後，得到適當的營養及保持健康生活型態以預防疾病的復發是必要的。

關鍵字：乳突瘤、脂肪酸、微量營養素、免疫不全、免疫營養。