The Turkish Journal of Pediatrics 1995; 37: 193-200

VITAMIN A LEVELS OF CHILDREN WITH MEASLES IN ANKARA, TURKEY*

*Şükrü Hatun MD***, *Tahsin Teziç MD****, *Benal Kunak MD***
*A. Bülent Cengiz MD***

SUMMARY: Hatun Ş, Teziç T, Kunak B, Cengiz AB. (Department of Pediatrics, Dr. Sami Ulus Children's Hospital, Ankara, Turkey). Vitamin A levels of children with measles in Ankara, Turkey. Turk J Pediatr 1995; 37: 193-200.

Recent studies show that vitamin A levels decrease during measles and that vitamin A therapy can improve measles outcome in children in the developing world. Vitamin A levels of children with measles have not been studied before in Turkey. Therefore we measured serum vitamin A levels in 21 children with measles and compared the results with "sick" and "healthy" control groups. The mean vitamin A levels in children with measles were markedly lower than in the "sick" and "healthy" control groups (p: 0.001). Vitamin A levels in children with measles ranged from 1.3 to 32 µg/dl; 11 (52%) were vitamin A deficient (< 10 µg/dl). This frequency among Turkish children supports evaluation of vitamin A status as a part of acute management of measles in Turkey. Clinicians may wish to consider vitamin A therapy for children with measles according to WHO recommendations. *Key words: vitamin A, measles, vitamin A deficiency, Turkey.*

The anti-infectious effect of vitamin A was pointed out by Green and Mellanby in 1928[1], and four years later Ellison[2] showed the potential benefit of vitamin A in measles treatment. Vitamin A, which has not drawn the attention of research thereafter, became popular again in the 1980s with the efforts of Alfred Sommer et al[3, 4]. Studies done for the last fifteen years have showed that vitamin A support may have a significant role both in reducing child mortality and in measles treatment[5-8].

Research investigating the relationship between measles and Vitamin A can be classified into three groups:

1. The first group of research points out that xerophthalmia usually follows measles, and measles is the precipitating factor for half of childhood blindness cases in Africa[9, 10].
2. The second group of research draws attention to the fact that during measles infection, the serum vitamin A level is low, leading to increased mortality and morbidity from measles[11-13].
3. In the third group of research it is shown that administering high-dose vitamin A to children with measles decreases mortality up to 50 percent[14, 15].

---

* From the Department of Pediatrics, Dr. Sami Ulus Children's Hospital, Ankara.

** Pediatrician, Dr. Sami Ulus Children's Hospital.

*** Professor of Pediatrics, Dr. Sami Ulus Children's Hospital.

As a result, the World Health Organization (WHO) and UNICEF published a report about vitamin A therapy in measles in 1987[16]. This report admits that vitamin A deficiency is a public health problem, and for those communities where mortality related to measles is greater than one percent, recommends routine vitamin A therapy, for children with measles (100,000 IU for children less than 12 months of age, and 200,000 IU for those older than 12 months). After this recommendation, vitamin A levels were investigated in several developing countries, and vitamin A therapy for measles has been initiated.

Measles is still a major child health problem in our country. According to the Ministry of Health data, 35,000 children were reported as having measles in 1993[17]. The measles mortality rate is not exactly known in our country. Despite the report published by WHO/UNICEF in 1987, vitamin A therapy is not widespread in Turkey. Very few studies have examined vitamin A deficiency in children, and there is a lack of research on the vitamin A status of children with measles[18]. In this study, the objective was to determine the vitamin A status in children with measles in Ankara and then to assess the necessity of vitamin A therapy in our country.

Material and Methods

Twenty-one patients seen at Dr. Sami Ulus Children's Hospital with a diagnosis of measles from November 1993 through March 1994 were considered for enrollment. The diagnosis of measles was made on clinical grounds. Children receiving vitamin A supplements in an amount greater than twice the recommended daily allowance were excluded from the study. Anthropometric values at enrollment included weight for age and height for age according to Neyzi et al. Standards for Turkish Children[19].

After completing the informed consent form, 5 ml of blood was drawn by venipuncture within 72 hours of the onset of a rash. Serum was obtained by centrifugation and stored at -30 °C until analyzed (within two months). During all procedures, blood samples were protected from sunlight to prevent photodestruction of vitamin A. Vitamin A (as retinol) was measured by normal phase high-pressure liquid chromatography (Beckman Instruments, Inc Altex Scientific Operations, California 94710, USA) at Düzen Laboratory, Ankara.

Two control populations were also studied. Fourteen children without acute infections and twenty-one children with documented infections other than measles (five with purulent meningitis, seven with pneumonia, and two with urinary tract infection) were enrolled as "healthy" and "sick" control groups, respectively.

All values are reported as mean ± SD. Differences in proportions in the data were examined by chi square and Fisher exact chi square tests. Differences in the means were examined by student's two-tailed t test. The Turkey studentized range method

within a one-way analysis of variance was used to perform pair-wise comparisons. The homogeneity of variances was examined by Levene test. A two-way analysis of variance was performed with age as covariate, because an age effect was observed. All statistical analyses were performed using SPSS for Windows V 5.01.

Results

A total of 56 children were included in the study; 21 had measles, 14 had acute infections other than measles and 21 were healthy. The characteristics of these children are given in Table I. Sixty-two percent of the children with measles were younger than 24 months of age. According to anthropometric measurements, none of them was identified as having malnutrition. Age variation was significant between children with measles and the "healthy" control group (p: 0.03).

Table I: Characteristics of Children with Measles and Control Children

	Measles Group	Sick Control Group	Healthy Control Group	ANOVA *p*
n	21	14	21	
Age (months)	42.5 ± 38.7	35.2 ± 30.9	10 ± 1.8	0.01 (KW)
% Male	66.7	50	52.4	NS
Weight Percentile for age	27.2 ± 21.1	28.1 ± 23.2	35.2 ± 20.2	NS
Height Percentile for age	33.7 ± 22.8	36.4 ± 26.5	40.5 ± 14.8	NS
Retinol (µg/dl)	11.5 ± 6.5	22.1 ± 6.5	26.9 ± 6.4	0.001
No. with retinol < 20 µg/dl	19 (90.5%)	6 (42.9%)	2 (9.5%)	0.00001
No. with retinol < 10 µg/dl	11 (52%)	1 (7.2%)	0	0.00006

ANOVA: analysis of variance; KW: Kruskal-Wallis; NS: not significant.

In children with measles, 19 out of 21 (90.5%), in children with acute infections other than measles (sick control group), six out of 14 (42.9%) and in the healthy control group, two out of 21 (9.5%) serum retinol levels were measured to be less than 20 µg/dl. In 11 children with measles (52%) and one child in the sick control group (7.2%), serum retinol levels were measured as less than 10 µg/dl. All of the children in the healthy control group had serum retinol levels greater than 10 µg/dl. The age variation between children with measles and the healthy control group did not affect the variation in serum retinol levels (p: 0.001 after the effect of age variation is eliminated).

Twelve children with measles were diagnosed with pneumonia (Table II). There was no significant difference between the serum retinol levels of children with and without pneumonia (p: 0.33); however, while 75 percent of children with pneumonia had serum retinol levels of less than 10 µg/dl, this low level was measured in only 22.2 percent of those without pneumonia. The number of children

having pneumonia with serum retinol levels of less than 10 µg/dl was significantly higher than the number of children in the other group (p: 0.02). Of the 12 children with pneumonia, four had severe clinical symptoms and very low retinol levels (1.3, 4.0, 7,0 and 8.2 µg/dl). One of these four children died of respiratory arrest.

Table II: Vitamin A Levels in Children With Measles With and Without Pneumonia

	Retinol (µg/dl)	No.with Retinol < 20 µg/dl	No.with Retinol < 10 µg/dl
With pneumonia (n: 12)	10.3 ± 7.7	11 (91.7%)	9 (75%)
Without pneumonia (n: 9)	13.3 ± 4.4	8 (88.9%)	2 (22.2%)
p*	0.33	0.69	0.02

(*) Fisher exact chi square test.

Discussion

In recent years, the studies done particularly in Africa and Asia show that serum retinol levels are low (< 20 µg/dl) in children with measles[11-13]. In a longitudinal study undertaken in India including 32 children with measles, low levels of the vitamin were shown to be specific to the acute phase of the infection, returning to normal at the end of eight weeks[12]. In another study published recently, low levels of retinol measured in the acute phase increased during convalescence[20]. Low serum retinol levels were first considered to be a result of malnutrition, thus more a problem of developing[21]. But surprisingly, in a recent study done in three different regions of the United States (U.S.) the serum retinol level was found to be low even in well-nourished children with measles[20, 22, 23]. Hence, the American Academy of Pediatrics suggested vitamin A therapy in accordance with WHO's recommendation[24]. Serum retinol levels of children with measles from various countries are given in Table III.

Table III: Vitamin A Status of Children With Measles in Various Countries

Country	n	Retinol (µg/dl)	No.with Retinol < 20 µg/dl	No.with Retinol < 10 µg/dl	References
Long Beach, USA	20	24.06 ± 12.03	10 (50%)	?	Arrieta CA et al[22].
Wisconsin, USA	114	16.61 ± 5.15	82 (72%)	?	Butler CJ et al[23].
Thailand	25	12 ± 0.9	(?)	8 (32%)	Varavithya W et al[11].
South Africa	31	11.73 ± 1.05	?	?	Coutsoudis A et al[34].
Zaire	283	5-63 (median, 8)	?	164 (58%)	Markowitz LE et al[13].
India	153	11.5 ± 0.44	?	?	Reddy V et al[12].
Ankara, Turkey	21	11.5 ± 6.5	19 (90.5%)	11 (52%)	

In our study, serum retinol levels were measured during the acute phase of measles and were found to be less than 20 µg/dl in 90.5 percent patients, and less than 10 µg/dl in 52 percent. Mean retinol levels of our patients and the degree of low levels are similar to the results of studies done in Africa and Asia (Table III). It is well known that vitamin A deficiency is a major public health problem in many countries of Africa and Asia. In a recent study done in our country, serum retinol levels were measured as low (< 20 µg/dl) in 60.7 percent of children with recurrent lower respiratory tract infections and/or diarrhea[25]. In another study done in the Sivas region including 100 children with malnutrition, 15 percent were found to have some kind of visual defect due to hypovitaminosis A[26]. Considering this information, a general vitamin A deficiency in the child population may be an important component of the very low levels of vitamin A measured in our study. However, as pre-measles levels of vitamin A were not measured in this study, it is not possible to draw conclusions. According to a study done in Zaire on 283 children with measles, a vitamin A level of less than 10 µg/dl significantly increases mortality, especially for children under the age of two[13]. But, as our study group was small and there was only one death, we cannot correctly discuss the impact of vitamin A deficiency on mortality.

The reason for low serum retinol levels in children with measles is unclear. This low level was previously explained by the exacerbation of the deficiency state due to the disease. However, in the study done in the U.S., serum retinol levels were measured as low even in well-nourished children with measles, and this low level was attributed to an acute decrease in the level of proteins (prealbumin and retinol binding protein) which mobilize retinol from the liver[24]. This view is supported by the fact that during convalescence, serum retinol levels return to normal without vitamin A administration[12, 22]. The finding of low retinol levels in other acute infections leads us to consider retinol as having a role of negative acute phase reactant in infections[27]. However, the finding that retinol levels are significantly lower during measles compared to other infections signifies that low levels are specific for measles[22]. Whatever the reason may be, during the acute phase of measles, serum retinol levels decrease independent of the nutritional status of the child, and the low level affects the outcome of the infection[21].

In our study, serum retinol levels of children with measles were significantly lower than those with other infections and healthy children. This result supports the idea that a low level of vitamin A is associated with a mechanism specific to measles, rather than being a general effect of infections[21]. However, it is worth mentioning that the children in the sick control group had significantly lower vitamin A levels than those of healthy children. Similar results have been published in the U.S.[22]. These findings point to the need for further research regarding the levels of vitamin A in infections other than measles and their clinical significance.

The clinical significance of low serum retinol levels and measles outcome with vitamin A therapy has been stressed by previous research[21, 24]. It is well known that children with measles frequently develop xerophthalmia. Studies from Asia and Africa show that measles plays an important role in childhood blindness[9, 10]. In addition to studies which have uncovered the association between measles and xerophthalmia, recent studies have shown that low levels of serum retinol are associated with the severity of measles. Markowitz et al.[13], in their Zaire study, showed that vitamin A deficiency significantly increases the mortality of children with measles, particularly for those under the age of 24 months. Similarly, in two studies from the U.S., low levels of vitamin A were shown to cause increased severity and morbidity of measles[20, 23]. The mechanism by which vitamin A depletion exacerbates measles infection is unknown. In experimental models, vitamin A deficiency impairs cellular immunity[28], delayed type hypersensitivity[29] and antibody production[30, 31]. Animal experiments indicate that vitamin A deficiency is associated with thymus atrophy and antibody production defects[32, 33]. In a study done in Indonesia, the ratio of CD4/CD8 was found to be low, and this low level could be corrected by vitamin A support[32]. Additionally, in recent studies done in the U.S. and South Africa on children with measles, it was pointed out that in children with low vitamin A levels, measles-specific antibodies were also in low levels, and could be restored by giving vitamin A[20, 34].

In our study, the presence or absence of pneumonia was considered to be a measure of the severity of measles. Despite the fact that serum retinol levels of children with pneumonia were not significantly different from those without pneumonia, 75 percent of the children with pneumonia had serum levels of less than 10 µg/dl. Although the number of cases is low, these findings still show an association between the severity of measles and serum retinol levels of less than 10 µg/dl (Table II). In one study done recently in the U.S., the mean level of serum retinol was lower in children with measles who were hospitalized and had pneumonia[23].

The effect of vitamin A therapy on mortality and morbidity in children with measles has been assessed with controlled studies. Barclay et al.[14], in a double-blind study, compared the effect of high-dose vitamin A (200,000 IU two days in a row) with that of a placebo[14]. In this study, measles mortality was reduced by vitamin A therapy, particularly for children under two years old. Vitamin A therapy was shown to reduce measles mortality by Hussey and Klein[15] in a 1990 study, and to reduce measles morbidity by Coutsoudis et al.[34] in a 1992 study. Hence, the American Academy of Pediatrics is now recommending vitamin A therapy for measles[24].

In conclusion, serum vitamin A levels are significantly low in children with measles in our country, and this low level is associated with the severity of disease. When recommendations from both WHO and the American Academy of Pediatrics are

taken into consideration, vitamin A therapy should be given routinely to children with measles in our country.

Acknowledgements

We thank Prof. Yahya Laleli, the owner of Düzen Laboratory, Gülveren Taşkın for her assistance in measuring serum vitaminn A levels, and Dr. Oktay Özdemir for his assistance in statistical analysis.

REFERENCES

1. Green HN, Mellanby E. Vitamin A as an anti-infective agent. Br Med J 1928; 111: 691-696.
2. Ellison JB. Intensive vitamin therapy in measles. Br Med J 1932; 11: 708-711.
3. Sommer A, Tarwotjo I, Hussaini G, Susanto D. Increased mortality in children with mild vitamin A deficency. Lancet 1983; 2: 585-588.
4. Sommer A, Tarwotjo I, Djunaedi E, et al. Impact of vitamin A supplementation on childhood mortality: a randomized controlled community trial. Lancet 1986; 1: 1169-1173.
5. Glasziou PP, Mackerras DE. Vitamin A supplementation in infectious diseases: a meta-analysis. Br Med J 1993; 306: 366-370.
6. Fawzi WW, Chalmers TC, Herrera MG, Mosteller F. Vitamin A supplementation and child mortality. JAMA 1993; 269: 898-903.
7. Editorial. Vitamin A for measles. Lancet 1987; 1: 1067-1068.
8. Sommer A. Vitamin A, infectious disease, and childhood mortality: a solution? J Infect Dis 1993; 167: 1003-1007.
9. Chirambo MC, Ezra DB. Causes of blindness among students in blind school institutions in a developing country. Br J Ophthalmol 1976; 60: 665-668.
10. Foster A, Sommer A. Childhood blindness from corneal ulceration in Africa: causes, prevention, and treatment, Bull WHO 1986; 64: 619-623.
11. Varavithya W, Stoecker B, Chaiyaratana W, Kittikool J. Vitamin A status of Thai children with measles. Trop Geogr Med 1986; 38: 359-361.
12. Reddy V, Bhaskaram P, Raghuramulu N, et al. Relationship between measles, malnutrition, and blindness: a prospective study in Indian children. Am J Clin Nutr 1986; 44: 924-930.
13. Markowitz LE, Nzilambi N, Driskell WJ, et al. Vitamin A levels and mortality among hospitalized measles patients, Kinshasa, Zaire. J Trop Pediatr 1989; 35: 109-112.
14. Barclay AJ, Foster A, Sommer A. Vitamin A supplements and mortality related to measles: a randomised clinical trial. Br Med J 1987; 294: 294-296.
15. Hussey GD, Klein M. A randomized, controlled trial of vitamin A in children with severe measles. N Engl J Med 1990; 323: 160-164.
16. Joint WHO/UNICEF Statement. Vitamin A for measles. Wkly Epidem Rec 1987; 19: 133-134.
17. Eker L. Director of expanded programme on immunization, Ministry of Health Turkey (Personal comminication), 1994.
18. Hatun Ş, Teziç T. Vitamin A and Child Health. Çocuk Sağlığı ve Hastalıkları Dergisi 1994, 37: 167-174.
19. Neyzi O, Binyıldız P, Alp H. Türk Çocuklarında Büyüme-Gelişme Normları I. Tartı ve Boy Değerleri. İstanbul Tıp Fakültesi Mecmuası 1978; 41: 74.
20. Frieden RT, Sowell LA, Henning KJ, Huff DL, Gunn RA. Vitamin A levels and severity of measles (New York City). Am J Dis Child 1993; 146: 182-186.

21. Hussey GD, Klein M. Measles-induced vitamin A deficiency. Ann NY Acad Sci 1992; 669: 188-194.

22. Arrieta AC, Zaleska M, Stutman HR, Marks MI. Vitamin A levels in children with measles in Long Beach, California. J Pediatr 1992; 121: 75-80.

23. Butler JC, Havens PL, Sowell AL, et al. Measles severity and serum retinol (vitamin A) concentration among children in the United States. Pediatrics 1993; 91: 1176-1181.

24. Committee on Infectious Diseases. Vitamin A treatment of measles. Pediatrics 1993; 91: 1014-1015.

25. Büyükgebiz B, Özalp I, Oran O. Investigation of serum vitamin A levels of children who had a history of recurrent diarrhoea and acute respiratory infections in Ankara. J Trop Pediatr 1990; 36: 251-255.

26. Tanzer F, Sağrak K, Çağlar Y. Eye findings and serum vitamin A levels in children with malnutrition from Sivas. Doğa 1986; 10: 65-71.

27. Kjolhede C, Rosales F, Caballero B, Gadomski A. Measles and low serum vitamin A values (letter). J Pediatr 1993; 122: 499-500.

28. Nauss KM, Mark DA, Suskind RM. The effect of vitamin A deficiency on the in vitro cellular immune response of rats. J Nutr 1979; 109: 1815-1823.

29. Smith SM, Levy NS, Hayes CE. Impaired immunity in vitaminn A-deficient mice. J Nutr 1987; 117: 857-865.

30. Hormon BG, Miller ER, Hoefer JA, Ullrey DE, Luecke RW. Relationship of specific nutrient deficiencies to antibody production in swine: vitamin A. J Nutr 1963; 79: 263-268.

31. Smith SM, Hayes CE. Contrasting impairments in IgM and IgG response of vitamin A deficient mice. Proc Natl Acad Sci USA 1987; 84: 5878-5882.

32. Krishnans, Buyan UN, Talwar GP, Romalingaswami V. Effect of vitamin A and protein calorie undernutrition on immune response. Immunology 1954; 27: 383-392.

33. Semba RD, Muhilal Ward BJ, Griffin DE, et al. Abnormal T-cell subset proportions in vitamin-A-deficient children. Lancet 1993; 341: 5-8.

34. Coutsoudis A, Kiepiela P, Coovadia HM, Broughton M. Vitamin A supplementation enhances specific IgG antibody levels and total lymphocyte numbers while improving morbidity in measles. Pediatr Infect Dis J 1992; 11: 203-209.