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Evaluation of Immunoglobulin Levels In Children Aged 1-5 Years With Recurrent Lower Respiratory Tract Infections

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ABSTRACT

Immunodeficiency plays a crucial role in the etiology of recurrent pneumonia. Humoral immunodeficiencies account for approximately 60% of all primary immunodeficiencies, and in such patients, antibody deficiencies are the leading cause of immunodeficiency. That study aimed to investigate the effect of immunoglobulin levels on the frequency of pneumonia episodes and the relationship between immunoglobulin levels and risk factors for pneumonia in children aged 1-5 years with recurrent pneumonia caused by humoral immunity.

The prospective study included a total of 92 randomly selected children aged 1-5 years, comprising a group of 70 patients hospitalized due to pneumonia and a group of 22 healthy controls who had no chronic diseases and infections.

Body height and weight were significantly lower in the patient group compared to the control group (p=0.012 and p=0.022, respectively). The mean breastfeeding duration was significantly lower (p=0.001), and the prevalence of exposure to environmental tobacco smoking (ETS) was significantly higher (p=0.018) compared to the control group. In the patient group, 65% of the participants had a deficiency of an immunoglobulin isotope and/or IgG subclasses in isolation or combination. IgG4 deficiency was the most common deficiency (38.5%), followed by IgG1 (21.4%), IgG2 (18.5%), IgA (15.7%), and IgG3 deficiency (12.8%), respectively.

Our results indicated that inadequate breastfeeding and environmental tobacco smoking prepare the ground for pneumonia, a significant cause of morbidity and mortality in children, and contributes to the recurrence of this disease. Humoral immunodeficiencies, a significant underlying cause of recurrent pneumonia that leads to growth retardation, may have different clinical manifestations.

Keywords: Humoral immune deficiency, childhood, recurrent lower respiratory tract infection

Introduction

Pneumonia is the leading cause of death in children under five years, accounting for 15% of all deaths in this population and claiming the lives of over 800,000 children under five years every year (1,2). In the same population, the rate of death caused by pneumonia decreased by 54% in 2018 compared to 2000 (3). Moreover, pneumonia is the most common cause of death in developing countries, and in these countries, the death rate from pneumonia is ten times higher than that of developed countries (4).

Some child deaths from pneumonia result from recurrent pneumonia, defined as two or more episodes within a year or three or more episodes of pneumonia in a lifetime (5). Recurrent pneumonia has been reported to be 6.4-11.3% among all pneumonia types (6-9). In children with recurrent pneumonia, various etiologies (69-92%) have been reported, and the most common etiologies have been shown to include aspiration pneumonia, asthma, immunodeficiency, and congenital heart disease. Moreover, immunodeficiency has been reported as the underlying cause of recurrent pneumonia in 3.1-17.75% of the cases (6,8,10,11). Immunodeficiency in children may have numerous primary and secondary factors (12). Notably, pneumonia results from common microorganisms and often has a severe course in children with an immune defect caused by humoral and cellular immunity. In these children, opportunistic microorganisms that do not cause disease in healthy hosts result in severe pneumonia (13). Lung infections in immunodeficient children have high mortality and are challenging to diagnose, thus requiring a prompt and multidisciplinary approach to the diagnosis and treatment (14).

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Humoral immunodeficiencies account for more than 50% of identified primary immunodeficiencies (15). Based on these data, the present study was designed to investigate the effect of immunoglobulin levels on the frequency of pneumonia episodes and the relationship between immunoglobulin levels and risk factors for pneumonia in children aged 1-5 years with recurrent pneumonia caused by humoral immunity.

Materials and Methods

Patient Selection: The prospective study included a total of 92 randomly selected children aged 1-5 years who presented to Bezm-i Alem Valide Sultan Vakıf Gureba Training and Research Hospital Pediatric Clinic between March 2009 and April 2010, comprising a group of 70 patients who were hospitalized due to recurrent pneumonia and a group of 22 healthy controls who had no chronic diseases and infections. The study was initiated after obtaining approval from the local ethics committee (Approval No: B.02.1.VGM.2.03.01.) and written consent from the parents/guardians of the participants in both groups. The patient group included patients who had experienced two or more episodes of pneumonia within a year or three or more episodes in a lifetime and had no other chronic diseases such as immunodeficiency, cystic fibrosis, and congenital heart disease. Pneumonia was diagnosed based on the presenting symptoms of the patients (cough, stertorous breathing, fever, cyanosis, and difficult breathing), physical examination findings (tachypnea, apnea, cyanosis, and stertorous breathing), and the detection of infiltration on lung radiography.

Laboratory Workup: Following blood collection, serum was separated and stored at -20 °C until analysis. The IgM, IgA, IgE, IgG, IgG1, IgG2, IgG3, and IgG4 levels were measured for each participant. The IgA, IgM, IgG, and IgG levels were measured using the nephelometric method, and total IgE levels were measured using the chemiluminescence method.

Statistical Analysis: Data were analyzed using NCSS 2007 (Kaysville, UT, USA). Descriptives were expressed as mean ± standard deviation (SD). Variables were compared using the Kruskal-Wallis test, subgroups were compared using Dunn's multiple comparisons test, pairwise comparisons were performed using the Mann-Whitney U test, and qualitative data were compared using the Chi-square test. A p-value of <0.05 was considered significant.

Results

The prospective study included 92 randomly selected children aged 1-5 years, comprising a group of 70 patients hospitalized due to pneumonia and 22 healthy controls with no chronic diseases and infections.

The patient group comprised 42 (60%) girls and 28 (40%) girls, and the control group included 12 (54.5%) boys and 10 (45.5%) girls. The mean age was 22.59 months in the patient group and 28.27 months in the control group. No significant difference was found between the two groups in mean age and gender distribution (Table 1).

Body height and weight were recorded in the patient group before hospitalization and during hospital admission in the control group. Mothers were queried about total duration of breastfeeding, exposure to environmental tobacco smoking (ETS), number of previous lung infections, number of previous hospitalizations, consanguineous marriage, history of immunodeficiency and death in siblings, prior atopic disorders, presence of recurrent upper respiratory tract infections (URTIs), comorbidities, and diseases that could cause lung injury including bronchiectasis and bronchiolitis obliterans syndrome. The prevalence of these conditions was recorded for both groups.

Body height and weight were significantly lower in the patient group compared to the control group (p=0.012 and p=0.022, respectively). In the patient group, the frequency of pneumonia episodes and the number of previous hospitalizations were significantly higher (p=0.0001 and p=0.0001, respectively), and the mean breastfeeding duration was significantly lower in the patient group (p=0.001) (Table 2).

There was no significant difference between the two groups concerning the prevalence of consanguineous marriage, immunodeficiency and death in siblings, personal and family history of atopic disorders, comorbidities, and lung injury. However, the prevalence of exposure to ETS and recurrent URTIs was significantly higher in the patient group compared to the control group (p=0.018 and p=0.014, respectively) (Table 3).

In our study, 65% of the patients had a deficiency of an immunoglobulin isotope and/or IgG subclasses either in isolation or combination. One patient had hypogammaglobulinemia, and only one patient had total IgG deficiency and partial IgA and IgG1+IgG2 deficiency. Two patients with selective IgA deficiency had IgG2 deficiency, and the other had IgG1+IgG4 deficiency. In 9 patients with partial IgA deficiency, three had IgG4 deficiency, 3 had IgG1+IgG2

Table 1. Mean Age and Gender Distribution

		Patient Group		Control Group		
Age (months)		22.59±12.16		28.27±13.13		t:-1.88 p=0.064
Gender	Male	42	60.0%	12	54.5%	χ^2:0,2
	Female	28	40.0%	10	45.5%	p=0.650

Table 2. Body Height, Weight, Number of Pneumonia Episodes, Duration of Breastfeeding, Number of Hospitalizations

	Patient Group	Control Group	t	p
Height (cm)	79.86±8.71	85.43±9.63	-2.55	0.012
Weight (kg)	10.83±2.89	12.41±2.39	-2.32	0.022
Pneumonia episodes	4.46±1.55	0.27±0.46	12.47	0.0001
Previous hospitalizations	2.24±1.1	0.09±0.29	9.08	0.0001
Duration of breastfeeding (months)	6.32±4.98	10.73±5.78	-3.45	0.001

deficiency, 1 had IgG2 deficiency, 1 had IgG1 deficiency, and only one had isolated partial IgA deficiency. In total, 11 (15.7%) patients had IgA deficiency. Of the 27 (38.5%) patients with IgG4 deficiency, 13 patients had isolated IgG4 deficiency, 3 had partial IgA deficiency, 1 had IgG1 deficiency, 1 had IgG2 deficiency, 2 had IgG2+IgG3 deficiency, and five patients had IgG3 deficiency. Nine (12.8%) patients had IgG3 deficiency combined with IgG2 and/or IgG4 deficiency. Fifteen (21.4%) patients had IgG1 deficiency, and 13 (18.5%) patients had IgG2 deficiency. Of the 15 (21.4%) patients with IgG1 deficiency, eight patients had isolated IgG1 deficiency, 2 had IgA+IgG2 deficiency, 1 had IgA+IgG2+IgG deficiency, 1 had IgA deficiency, 1 had IgG4 deficiency, and one patient had IgA+IgG4 deficiency. Of the 13 (18.5%) patients with IgG2 deficiency, three patients had isolated IgG2 deficiency, 2 had IgA deficiency, 2 had IgA+IgG1 deficiency, and 1 had IgA+IgG+IgG1 deficiency, 1 had IgG4 deficiency, 1 had IgG3 deficiency, and two patients had IgG3+IgG4 deficiency. Accordingly, IgG4 deficiency was the most common deficiency (38.5%), followed by IgG1 (21.4%), IgG2 (18.5%), IgA (15.7%), and IgG3 deficiency (12.8%), respectively.

No significant difference was found between the two groups concerning the mean IgM, IgE, and IgG1 subclass levels. In contrast, the mean IgA, IgG, IgG2, IgG3, and IgG4 subclass levels were significantly lower in the patient group than in the control group (p=0.0001, p=0.0001, p=0.003, p=0.0001, and p=0.0001, respectively). (Table 4) (Figures 1,2,3).

In terms of breastfeeding duration, patients were grouped as (i) no breastfeeding, (ii) <6 months, (iii) 6-12 months, and (iv) ≥12 months, and no significant difference was found among the groups about the mean IgM, IgA, IgE, IgG, IgG1, IgG2, IgG3, and IgG4 levels.

No significant difference was found between children exposed to and not exposed to ETS concerning the mean IgM, IgE, IgA, IgG, IgG2, IgG3, and IgG4 levels, while the mean IgG1 levels were significantly lower in children exposed to ETS (5.02±3.76; n=56) compared to non-exposed children (6.88±2.16; n=14) (p=0.026).

In terms of the frequency of pneumonia episodes, patients were divided into two groups as (I) 2-4 episodes and (II) ≥5 episodes, and no significant difference was found between the two groups in the mean IgM, IgA, IgE, IgG, IgG1, IgG2, IgG3, and IgG4 levels.

No significant difference was found between children with and without a history of recurrent URTIs in the mean IgM, IgA, IgE, IgG, IgG1, IgG2, and IgG4 levels. In contrast, the mean IgG3 levels were significantly lower in children with a history of recurrent URTI (0.32±0.24; n=14) than the children without a history of recurrent URTI (0.65±0.75; n=54) (p=0.048).

No significant difference was found between children with and without a personal history of atopic disorders in the mean IgM, IgA, IgE, IgG1, IgG2, and IgG3 levels, while the mean IgG (682.93±208.27; n=60) and IgG4 (0.14±0.21; n=60) levels were significantly lower in non-atopic than atopic children (852.2±242.95 and 0.6±0.91; n=10, respectively) (p=0.025 and p=0.033, respectively)

No significant difference was found between children with and without a family history of atopic disorders concerning the mean IgM, IgA, IgG, IgG1, IgG3, and IgG4 levels, whereas the mean IgE levels were higher in children with a family history of atopic disorders,

Table 3. Additional Demographic and Clinical Characteristics

		Patient Group		Control Group		
Consanguineous marriage	No	32	45.7%	14	63.6%	χ^2:2.1
	Yes	38	54.3%	8	36.4%	p=0.143
Death of siblings	No	64	91.4%	22	100.0%	χ^2:2
	Yes	6	8.6%	0	0.0%	p=0.156
History of immunodeficiency in siblings	No	66	94.3%	22	100.0%	χ^2:1.3
	Yes	4	5.7%	0	0.0%	p=0.252
Environmental tobacco smoking	No	14	20.0%	10	45.5%	χ^2:5.6
	Yes	56	80.0%	12	54.5%	p=0.018
Personal history of atopy	No	60	85.7%	20	90.9%	χ^2:0.39
	Yes	10	14.3%	2	9.1%	p=0.528
Family history of atopy	No	62	88.6%	20	90.9%	χ^2:0.09
	Yes	8	11.4%	2	9.1%	p=0.759
Comorbidities	No	68	97.1%	22	100.0%	χ^2:0.64
	Yes	2	2.9%	0	0.0%	p=0.423
History of recurrent URTIs	No	54	77.1%	22	100.0%	χ^2:6
	Yes	16	22.9%	0	0.0%	p=0.014
Lung injury	No	64	91.4%	22	100.0%	χ^2:2
	Yes	6	8.6%	0	0.0%	p=0.156

URTIs: Upper respiratory tract infections

Table 4. Laboratory Parameters

	Patient Group	Control Group	MW	p
IgM (mg/dL)	119.25±58.67	102.64±36.2	737.5	0.766
IgA (mg/dL)	47.63±39.44	90.96±13.4	192	0.0001
IgE (IU/mL)	113.07±224.22	36.59±35.5	687	0.447
IgG (mg/dL)	707.11±219.88	1095.77±215.91	174.5	0.0001
IgG1 (g/L)	5.39±3.57	5.9±1.46	661.5	0.320
IgG2 (g/L)	1.49±1.11	2.03±0.71	448	0.003
IgG3 (g/L)	0.58±0.68	1.32±0.38	140	0.0001
IgG4 (g/L)	0.21±0.41	0.76±0.39	144.5	0.0001

albeit not significantly. Moreover, the mean IgG2 levels were significantly lower in children without a family history of atopic disorders (1.37±0.98; n=62) than the children with familial atopy (2.43±1.61; n=8) (p=0.042)

Moreover, no significant relationship was found between patients with 2-4 pneumonia episodes and patients with ≥5 episodes regarding consanguineous marriage and exposure to ETS.

Discussion

Pneumonia is the most common infectious cause of death in children worldwide (1). In some of these children, mortality results from recurrent pneumonia, which has been shown to have varying incidence rates (6.4-11.3%) (6-9). Recurrent pneumonia is defined as two or more episodes within a year or three or more episodes of pneumonia in a lifetime altogether, with clinical and radiographic clearance in between (5).

For recurrent pneumonia in children, varying etiologies and different diagnostic methods have been reported, with the most common etiologies including aspiration pneumonia, asthma, immunodeficiency, and congenital heart disease. Immunodeficiency has been reported in 3.1-17.75% of the patients (6-11,16,17).

In the present study, we investigated the relationship between immunoglobulin deficiencies and recurrent lung infections and the factors affecting the recurrence of lung infections in patients with humoral immunodeficiency, the most common subclass of immunodeficiency. The results indicated no significant difference in age and gender distribution

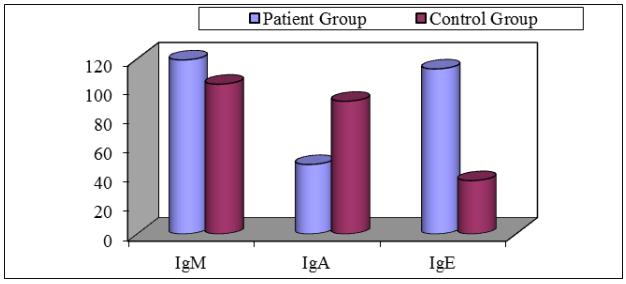

Fig. 1. IgM, IgA, and IgE levels (IgM, IgA: mg/dl; IgE: IU/ml)

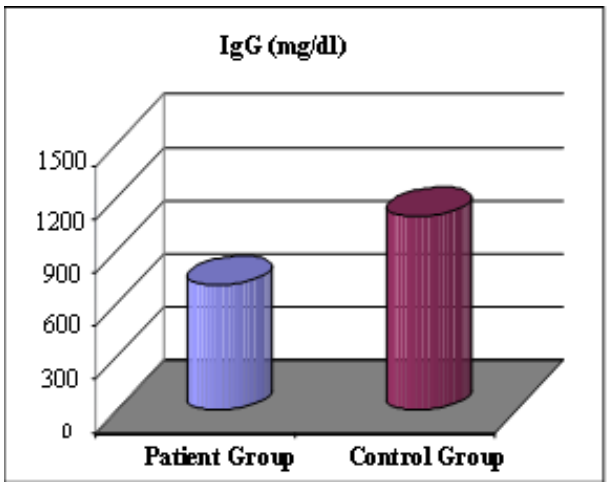

Fig. 2. IgG levels

between the two groups. Previous studies investigating children with recurrent pneumonia included patients with heterogeneous age distribution, and in those studies, most patients were aged less than two years (17,18). Similarly, 44 (62.8%) of the children in our study were nurslings (aged 1-2 years), implying that recurrent pneumonia is a significant cause of morbidity in nurslings.

Healthy children may present with respiratory symptoms after one year of age. Children with these infections do not require hospitalization, respond well to standard treatments, show average growth, and usually have long well-being periods between the episodes (19). In our study, body height and weight were lower, and the mean frequency of pneumonia episodes and the mean number of previous hospitalizations associated with these episodes was significantly higher in the patient group compared to the control group.

Cigarette smoking suppresses the expression of T cells, which are components of immunity, inhibits the activity of natural killer cells and alveolar macrophages, and reduces IgG and IgA serum levels (20). In the literature, it was shown that pneumonia was the most common respiratory disease in children in case of parental smoking and indoor exposure (21), while community-acquired pneumonia severity and hospital stay were longer in those who smoked more

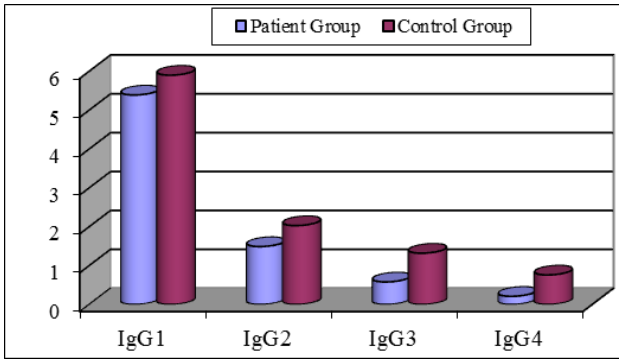

Fig. 3. IgG subclass levels (g/l)

than two cigarettes at home (22). Capanoglu declared that exposure to ETS was more common in children with recurrent pneumonia than in healthy controls (23). However, in our study, no significant relationship was found between the frequency of pneumonia episodes and exposure to ETS, although the mean IgG1 levels were lower in children with recurrent pneumonia than in healthy children. A previous study declared that total IgG levels and IgG2 subclass levels were significantly lower in asymptomatic smokers and smokers with chronic bronchitis and recurrent exacerbations (24).

Both WHO and UNICEF recommend that children begin breastfeeding within the first hour after birth and be particularly breastfed for the first six months of life (25). Accumulating evidence suggests that breastfeeding significantly reduces severe respiratory infections, mortality, and hospitalization (26). Duijts et al. also found that children exclusively breastfed until six months had lower risks of lower URTIs than children exclusively breastfed until four months (27). In the present study, the mean duration of breastfeeding was significantly lower in children with recurrent pneumonia (6.32±4.98 months) compared to healthy controls (10.73±5.78 months), which confirms the protective role of breastfeeding against respiratory tract infections. However, there was no significant difference between never-breastfed children and those breastfed for six months or longer regarding Ig levels.

Quantitative immunoglobulins testing is an important screening test for detecting primary and secondary immunodeficiencies (28). The most common indications for this testing in pediatric clinical practice are severe, persistent, opportunistic, and recurrent infections. On the other hand, antibody deficiency accounts for roundly 60% of all primary immunodeficiencies (15,29).

IgA deficiency is the most common primary immunodeficiency disease (30). Though IgM deficiency is a rare isotope deficiency, it can present either in isolation or in combination with other

antibody deficiencies in respiratory tract infections (31). IgA deficiency and a deficiency of one or more IgG subclasses are risk factors for more severe and recurrent infections (32). IgG is divided into four subclasses based on the position and number of disulfide bonds and the IgG in the bloodstream is 60-70% IgG1, 20-30% IgG2, 5-8% IgG3, and 1-3% IgG4, and these amounts vary with age (28,33). The age at which each IgG subclass achieves adult levels varies among communities (34).

In our study, 65% of the patients had a deficiency of an immunoglobulin isotope and/or IgG subclasses either in isolation or combination. A previous study evaluated the serum levels and the role of immunoglobulin in recurrent respiratory tract infections in children and reported this rate at 58% (35). Another study reported that a deficiency in one or more IgG subclasses was detected in 57% of infants with recurrent bronchitis (36). Another study evaluated the levels of Ig isotopes and IgG subclasses and detected various immunoglobulin deficiencies in 35% of the patients, mainly including IgG4 deficiency (17.5%) and IgA deficiency (10.8%) (37). In our study, 38.5% of the patients had IgG4, 21.4% had IgG1, 18.5% had IgG2, 15.7% had IgA, and 12.8% had IgG3 deficiency isolated or combined with other IgG subclasses. Accordingly, deficiency of IgG subclasses was the most common deficiency among our patients, which was consistent with the findings of De Baets et al. and Coskun et al., who reported that the IgG4 deficiency was the most common deficiency in their patients.

The IgG1 deficiency has been associated with a lifelong raised susceptibility to pyogenic infection (38). A previous study evaluated 54 adult patients with IgG1 deficiency and reported that 90% of the patients had a respiratory tract infection in two or more sites, including sinusitis in 92.6%, bronchitis in 77.8%, and pneumonia in 53.7% of the patients (39). In our study, the IgG1 deficiency was detected in 21% of the patients, either isolated or combined with other IgG subclasses.

Numerous studies have indicated that the IgG2 deficiency is more commonly identified in children with recurrent infections than in other subclasses' deficiencies (38,40) and is more usually seen in children under four years (41,42). In some other studies, these notions have been attributed to the fact that pathogens such as *Haemophilus influenza* (*H. influenza*), Pneumococci, and Meningococci and the antibodies against polysaccharide capsules are frequently seen in IgG2 subclasses (28,42-44).

IgG3 is known to have a significant role in responding to respiratory viral infections. Moreover, IgG3 is an essential factor in the immune response to *M. catarrhalis*, a well-known cause of recurrent sinusitis (45). Deficiencies of IgG3 subclasses are the most common deficiencies of immunoglobulin subclasses in adults with recurrent upper and lower respiratory tract infections (38). Similarly, in our study, IgG3 levels were significantly lower in children with recurrent pneumonia than in healthy children.

IgA deficiency is inherent in IgG subclass deficiencies, particularly with IgG2 or IgG4 subclass deficiencies (28,46). Numerous studies have also indicated that the incidence of IgG2 subclass deficiency, which has the most significant role in identifying carbohydrate antigens, is increased in patients with symptomatic IgA deficiency (50). In our study, the most common combined deficiency was IgG3+IgG4 deficiency, followed by IgA+IgG2 deficiency.

In a recent study, Montella et al. evaluated the risk factors in children with recurrent pneumonia and found that 25% of the patients had a history of atopy (11). Atopy is commonly seen with selective IgA deficiency (30). In our study, the IgE levels were higher in children with a family or personal history of atopy than in healthy controls, though the difference was not significant. However, the IgG and IgG4 levels were significantly higher in children with a personal history of atopy, and the IgG2 levels were significantly higher in children with a family history of atopy.

Our results confirmed that humoral immunodeficiencies in children are significantly associated with recurrent respiratory tract infections and have a significant role in long-term outcomes in such patients. Inadequate breastfeeding was found to contribute to the recurrence of infections, and some other factors, including exposure to environmental tobacco smoking and personal and/or family history of atopy, were found to be related to a raised incidence of deficiencies of certain Ig isotopes and a high frequency of recurrent respiratory tract infections. Numerous laboratory tests can achieve the measurement of Ig isotopes. Although these tests may vary across countries and laboratories, the assessment of humoral immunity in children with recurrent pneumonia should include the measurement of not only Ig levels but also Ig subclass levels.

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