Otological Findings in Pediatric Patients with Hypogammaglobulinemia

Marzieh Tavakol[1], Ali Kouhi[2], Hassan Abolhassani[3,4], Alireza Ghajar[3],
Mohsen Afarideh[3], Shervin Shahinpour[3], and Asghar Aghamohammadi[3]

[1] *Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases
(NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[2] *Otorhinolaryngology Research Center, Amir Alam Hospital, Department of Otolaryngology,
Tehran University of Medical Sciences, Tehran, Iran*
[3] *Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center,
Tehran University of Medical Sciences, Tehran, Iran*
[4] *Division of Clinical Immunology, Department of Laboratory Medicine, Karolinska Institutet at the Karolinska
University Hospital Huddinge, Stockholm, Sweden*

ABSTRACT

The main clinical presentation of patients with primary antibody deficiency (PAD) incorporates upper respiratory tract infections comprising otitis media, sinusitis and pneumonia. This study was designed to investigate clinical and paraclinical otological complications in major types of PAD.

A cross sectional study was conducted on 55 PAD patients with diagnosis of selective IgA deficiency, common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA), and hyper IgM syndrome. All patients underwent otological examinations, audiometry, and auditory brain stem response.

Otological complications were detected in 54.5% of PAD patients. Conductive hearing loss was the main finding amongst PID patients (73.3%) followed by sensorineural hearing loss which was present in 8 cases. Otitis media with effusion (21.8%), chronic otitis media (27.2%), tympanosclerosis with intact tympanic membrane (5.4%) and auditory neuropathy (3.6%) were most important found complications. CVID and XLA patients with prophylactic usage of antibiotics had lower rate of audiological complications (p=0.04) and otitis media with effusion (p=0.027).

As our results showed, asymptomatic otological findings were not rare in PAD patients; therefore, a systematic otological investigation is recommended as an integral part of the management and follow-up of these patients.

Keywords: Chronic otitis media; Hearing loss; Hypogammaglobulinemia; Primary antibody deficiency

Corresponding Author: Asghar Aghamohammadi, MD, PhD;
Children's Medical Center Hospital, Tehran 14194, Iran.

Tel: (+98 21) 6642 8998, Fax: (+98 21) 6692 3054, E-mail:
aghamohammadi@sina.tums.ac.ir

INTRODUCTION

Primary antibody deficiency (PAD) represents the around 1:500-1:25,000 in all populations.[5-9]

Unanimously, most common types of PAD account for the approximately half of all primary immunodeficiency diseases (PID).[1-4] Selective IgA deficiency (SIgAD), common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA) and hyper IgM syndrome (HIgM) are identified as the major types of PADs amongst clinicians.[6]

The clinical manifestations of PADs are highly variable and both infectious and non-infectious complications can occur due to delay in diagnosis and inappropriate management of these patients. The main infections incorporate upper and lower respiratory tracts including sinusitis, otitis media, pneumonia and less frequently sepsis and meningitis.[10] Several studies documented that sinopulmonary recurrent infections occur in 70-90% of patients with antibody deficiency during the course of disease[11, 12]; commonly caused by pyogenic bacteria, such as *Haemophilus influenza* and *Streptococcus pneumonia*.[2, 3, 12-14]

In addition, ear, nose, and throat (ENT) infections, especially upper respiratory infections can frequently be the first presenting symptom in these patients. In antibody deficient patients, approximately 50% of cases present general physicians and pediatricians with ENT symptoms.[10, 15, 16] Based on previous reports, otitis media was shown to be the most frequent presenting symptom (32%) in PAD followed by sinusitis (15%) and mastoiditis (3.6%). Early diagnosis and appropriate treatment leads to reduction of episodes of otitis per year in each XLA patient from 3.6 to 0.7 episodes per year. This decrease was about 5.8 folds in CVID (3.8 to 0.65) and 1.4 folds in SIgAD (2.2 to 1.6).[3, 15]

Chronic otitis media and deafness are the most common long-term problems of PAD cases worldwide and significantly impacts quality of life in both children and adults.[17] These data suggest that otological complications and different types of hearing loss (conductive, sensory neural or mixed) associated with upper respiratory mucosal infection might be a relatively common finding in patients with PAD.

Few studies, however, have considered prevalence of ENT complications in PID patients through comprehensive evaluations of hearing impairment in these patients[18]. In this study, we addressed this issue by performing audiological examination and paraclinical tests to evaluate the prevalence of otological complications and hearing impairments in PAD patients.

MATERIALS AND METHODS

Patients

Approval for this study was obtained from the institutional ethical review boards of the Tehran University of Medical Sciences (TUMS). The immunodeficiency clinic at the Children's Medical Center affiliated to the TUMS, Tehran, Iran is a referral center for both pediatric and adult PAD patients and provides comprehensive and multidisciplinary health care services for the patients.

We recruited all patients with the diagnosis of PAD; who attended for treatment and follow-up sessions during 2010-2012 to conduct a hospital-based cross sectional study concerning the prevalence of hearing impairments. Eligibility factor for inclusion of patients in this study was the diagnosis of PAD based on the Pan American Group for Immunodeficiency (PAGID) and European Society for Immunodeficiencies (ESID) criteria.[19, 20] Patients were excluded if they had any recognized functional or anatomical malformation of nervous system affecting auditory function (e.g. Arnold-chiari malformation) or any other underlying cause of acquired hearing loss (e.g. jaundice, history of ear-damaging trauma, congenital infection, hypothyroidism, and diabetes mellitus). All patients were negative regarding their history of diuretics, salicylates or cis-platin usage. Severity score of disease was measured based on the previous criteria for weighing of complication of patients.[21-23] Based on intensity of patient management as indicated by quality of treatment, patients were separated into two groups: well treated (<3 missed months for visits and intravenous immunoglobulin (IVIg) therapy) and irregularly treated (>3 missed months for visits and IVIg therapy). Written informed consents were obtained from the adult patients and children's parent(s). Other clinical, Immunologic (eg. Immunoglobulin levels and lymphocyte subsets) and paraclincal (eg. spirometry, computed tomography) data of patients were extracted from Iranian PID registry according to the published methods [14,23].

Audiological Tests

Patients were referred to Amir-Alam hospital (tertiary referral center for ENT diseases, affiliated to TUMS) for audiological investigations. All of the patients underwent clinical examination using an operating microscope. Pinna, external auditory canal, tympanic membrane integrity or sclerosis, middle ear aeration, and any other otological pathology were assessed.

In history taking and examination, otitis media with effusion (OME) and chronic suppurative otitis media were evaluated separately.

Tuning fork tests were done using 512 and 1024 Hz diapasons. Tympanic membrane movement was checked by pneumatic otoscope. Vestibular system status was evaluated by physical examination including dix-hallpike, head shake, and head thrust tests. Hearing status was assessed by pure tone audiometry and speech audiometry (Madsen, Astera, Denmark and Madsen, midimate 622, Denmark). Bone- and air-conducting hearing threshold (250 Hz, 500Hz, 1kHz, 2 kHz, 4 kHz, 6 kHz, and 8 kHz), speech reception threshold (SRT), and speech discrimination score (SDS) were measured. Impedance audiometry (Madsen, Zodiac 901, Denmark) parameters were noted as follows: static compliance, middle ear pressure, and external canal volume. Acoustic reflexes were recorded with ipsilateral and contralateral stimulation. Auditory brain stem response (ABR) was performed for all of the patients (GN-otometrics, ICS-Chartr EP, Denmark). Wave I, III, and V latencies, inter-peak latencies, and wave forms were recorded and analyzed. Also conductive hearing loss (CHL) and sensorineural hearing loss (SNHL) were evaluated based on the findings of above mentioned tests. CHL occurs because of a mechanical problem in the outer or middle ear (sound waves air conduction is disrupted along the route through the outer ear, tympanic membrane, or middle ear) and can be found by sound localizes to affected ear in Weber test and is negative on bone/air gap in Rinne test and bone conduction>air conduction in bone- and air-conducting hearing threshold test. Sensorineural hearing loss occurs when the tiny hair cells that detect sound in the ear are injured during investigation by sound localized to normal ear in Weber test and positive Rinne test; air conduction > bone conduction in bone- and air-conducting hearing threshold test in which both air and bone conduction are decreased equally, but the difference between them is unchanged.

The results of all otological examinations were recorded in a previously designed questionnaire and were compared in different groups of patients based on type of PAD disease.

Statistical Analysis

Statistical analysis was performed using a commercially available software package (SPSS Statistics 17.0, Chicago, Illinois). One-sample Kolmogrov-Smirnov test estimated whether data were normally distributed. Parametric and nonparametric analyses were performed based on the finding of this evaluation. A p value of 0.05 or less was considered statistically significant.

RESULTS

A total of 55 patients comprising of 42 males (76.4%) and 13 females (23.6%) were enrolled in this study. Distribution of PAD patients in our study consisted of 24 patients with CVID, 16 patients with XLA, 5 patients with HIgM syndrome, 5 patients with ataxia telangiectasia (AT) and 5 patients with SIgAD. Mean age of these patients was 13.9±6.6 years, median age of onset was 1 (range, 0-10) years, median diagnostic delay was 2.45 (range 0-16) years, mean age at time of diagnosis was 5.2±3.2 years, mean follow up duration was 8.0±5.4 years, and mean disease course duration was 11.6±6.7 years. Table 1 provides a general view on demographic information of PAD patients in our survey.

In medical history taking section, recurrent otitis media (ROM), more than 4 episodes of acute otitis media, annually, represented the most frequent clinical presentation at the time of diagnosis as manifested by several episodes in 35 out of 55 (63.6%) patients. We found no significant relationship between type of PAD and occurrence of ROM. History of previous otologic assessment was positive in only 24 patients (43.6%). History of aminoglycoside agent use for prophylactic purposes was positive in 2 subjects.

Based on physical examination, OME (12 patients) and COM (15 patients) were the most frequent complications in PAD patients (Table 2).

After tuning fork tests and other paraclinical evaluations, hearing loss were detected in 30 out of 55 (54.5%) patients. CHL constituteds the main otological finding (22 out of 30 patients; 73.33%) and 8 patients

(23.33%) had SNHL (Figure1). Only one CVID patient showed a mixed conductive and sensorineural hearing loss. Auditory neuropathy was found in 2 patients, one in CVID group and one in XLA. Table 2 depicts the mean ABR for PAD patients. The mean score of SDS and SRT in all PAD patients were 99.6±1.6 and 10.8±10.5, respectively (Table2). Pure tone audiometry results were illustrated based on each type of diseases in Figure 2.

Table1. Demographic data of 55 patients with primary antibody deficiencies

Parameters	CVID	XLA	HIgM	AT	SIgAD	Total
No. of patients	24	16	5	5	5	55
Male/ Female	17/7	16/0	5/0	2/3	2/3	42/13
Onset age; year (±SD)	2.30±3.11	1.80±1.82	4.40±3.43	2.30±3.56	2.00±1.54	2.33±2.75
Diagnosis delay; year (±SD)	4.31±3.43	2.80±1.72	2.80±4.65	3.00±2.34	0.5±1	3.31±3.04
Current age; year (±SD)	15.17±6.99	14.53±6.61	16.00±5.24	9.00±4.30	8.50±4.35	13.96±6.61
Diagnostic age; year (±SD)	6.13±3.74	4.53±2.58	5.20±2.86	5.40±2.30	2.50±1.91	5.23±3.20
Follow up; year (±SD)	7.95±5.59	9.73±6.11	9.20±1.92	3.60±3.28	6.00±4.54	8.01±5.41

CVID: common variable immunodeficiency; XLA: X-linked agammaglobulinemia; HIgM: hyper IgM syndromes; AT: ataxia telangiectasia; SIgAD: selective IgA deficiency.

Totally, ear problems were significantly higher in CVID patients compared to other PAD patients (p=0.02; OR $_{CVID/HIgM}$= 0.3, CI=0.1-0.92; OR $_{CVID/AT}$= 0.3, CI=0.1-0.92). Type of ear problem (SNH, CHL, p=0.37), frequency of COM (p=0.69), prevalence of OME (p=0.26), active COM with otorrhea (p=0.37), result of SRT, SDS and ABR were not statistically different among different groups of PAD patients.

Otological Manifestations of CVID

CVID cases with history of prophylactic antibiotic against common sinopulmonary microorganisms showed lower total ENT complications compared to remaining CVID patients (p=0.04). Surprisingly, presence of COM had direct association with presence of bronchiectasis in this type of PAD (p=0.01). Although two patients had positive history of ototoxic drug (aminoglycoside) consumption, otological evaluations were normal in one of them and the other one had CHL. From a total number of 4 patients with a history of bacterial meningitis, 3 of them suffered from CHL and none had SNHL.

Table 2. Otological investigations for 55 patients with primary antibody deficiency

Parameters	Total	CVID (N=24)	XLA (N=16)	HIgM (N=5)	AT (N=5)	SIgAD (N=5)	P-value
No. of patients with ear problems (%)	30 (54.5)	17(56.7) **	9(30)	1(3.3)	1(3.3)	2(6.6)	0.02*
Physical examination							
Chronic otitis media, N(%)	15(27.3)	6(25)	5(31.3)	2(40)	0	2(40)	0.57
Otitis media with effusion, N(%)	12(21.8)	8 (33.3)	2 (12.5)	0	1 (20)	1 (20)	0.39
Tympanosclerosis, N(%)	3(5.4)	1	2	0	0	0	0.64
Auditory Brainstem-Evoked wave latency							
Wave latency I, msec (mean±SD)	1.52±0.21	1.55±0.25	1.52±0.15	1.44±0.04	1.40±0.03	1.30±0.23	0.89
Wave latency III , msec (maen±SD)	3.58±0.23	3.61±0.26	3.58±0.2	3.69±0.19	3.40±0.12	3.27±0.17	0.59
Wave latency V, msec (mean±SD)	5.40±0.32	5.41±0.23	5.46±0.41	5.60±0.24	5.07±0.17	4.95±0.22	0.37
Audiometry							
Speech Discrimination Score (mean±SD)	99.61±1.68	99.89 ±0.45	99.58 ±1.44	99.8±0.2	98 ± 4.47	99.7±1.3	0.35
Speech Reception Threshold (mean±SD)	10.83±10.51	13.37±11.5	12.91±12	3.12±3.75	7±2.73	4.37±3.14	0.15

CVID: common variable immunodeficiency; XLA: X-linked agammaglobulinemia; HIgM:hyper IgM syndromes; AT: ataxia telangiectasia; SIgAD: selective IgA deficiency.   *: Significant difference or p<0.05   **: Significant difference or p<0.05 in post Hoc analysis with AT and HIgM
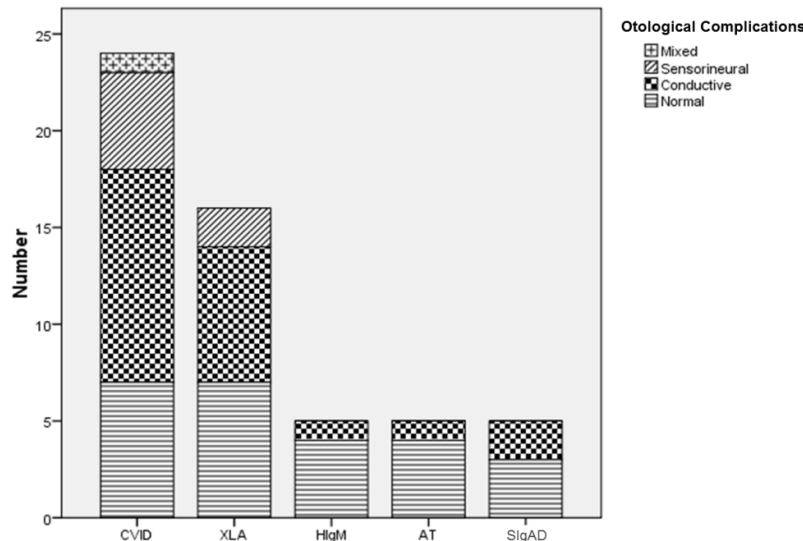
Figure 1. Distribution of otological complications among 55 patients with primary antibody deficiencies. CVID: common variable immunodeficiency; XLA: X-linked agammaglobulinemia; HIgM:hyper IgM syndromes; AT: ataxia telangiectasia; SIgAD: selective IgA deficiency.

The mean severity score of all 24 studied CVID patients equaled 69.3±44.9. Severity score of affected individuals without otological complications was 38.7±21.6 while the severity score of complicated subjects was 82.0±46.3 (p=0.012). Age at the onset of the disease (p=0.034) and lymphoproliferative complications (p=0.022) seemed to be significantly correlated with otological manifestations. Patients with early onset of disease and cases with polyclonal lymphocytic infiltrative phenotypes were more susceptible to CHL (p=0.008 and 0.013, respectively).

Significantly reduced number of WBCs were found significantly in cases with OME (p=0.04). Reverse CD4/CD8 ratio predicted the CHL disorder in CVID patients (p=0.012) and probable retro-cochlear pathologies (evident by abnormal mean SDS score, (p=0.014).

PTA results of children affected by CVID showed significant increase in thresholds in higher frequencies (4000 and 8000 AC threshold, p=0.05). Moreover, lymphoproliferative phenotype (p=0.034), bronchiectasis (p=0.05) and abnormal pulmonary function test (p=0.02), higher clinical severity score (p=0.024), and higher delay in diagnosis (p<0.001) had significant correlation with defective ABR examination in CVID patients.

Diagnostic delay demonstrated direct and significant correlation with wave I latency in ABR (p=0.001) which is congruent with middle ear pathology association with mismanagement of CVIDs.

Interestingly, CVID patients with records of ROM illustrated a significantly higher ABR wave latency in wave V (p=0.01). Diagnostic delay was also in significant correlation with probability of decreased hearing power, evident by abnormal SRT test (p=0.006). Intensity of patient management as indicated by quality of treatment was related with ABR wave I and III and V latency (p=0.01 and 0.003 and 0.04, respectively).

Otological Manifestations of XLA

Using prophylactic antimicrobial agents led to lower OME frequency in XLA patients (p=0.027).

XLA patients with poor quality of treatment had significantly higher rates of dry COM (p=0.01) and active COM with otorrhea (p=0.042) comparing with those who had regular visit and monthly IVIg replacement. Severity score was shown to be correlated with presence of ENT complications (p=0.034) and wave latency in ABR especially V wave (p=0.047).

Serum level of IgG is a subject of significant difference amongst ENT complicated and non-complicated XLA patients (p=0.21). Moreover different analytic methods showed association of lymphopenia with CHL (p=0.007), duration of disease with COM (p=0.049), and absolute count of T cells
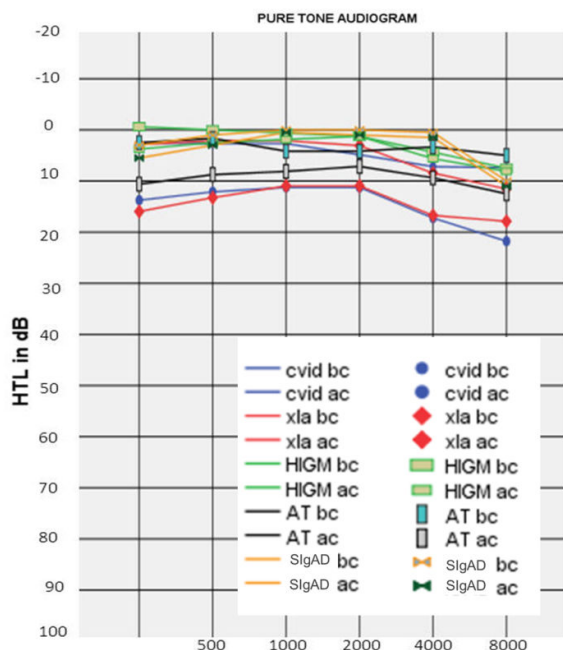
Figure 2. Mean bone and air conduction threshold among 55 patients with primary antibody deficiencies. CVID: common variable immunodeficiency; XLA: X-linked agammaglobulinemia; HIgM: hyper IgM syndromes; AT: ataxia telangiectasia; SIgAD: selective IgA deficiency.

with COM (p=0.05) in XLA group. The findings of this study supported significant direct association between abnormal spirometery and consequent PTA impairment (p=0.007). ABR test was abnormal in patients with higher duration of disease (p=0.01) as well as SRT results of XLA cases with high clinical score of severity (p=0.03).

Otological Manifestations of Other Types of PAD

The observed finding indicated association of serum IgA levels in AT patients with presence of ENT complications (p=0.01). Moreover in AT patients, severity score is a major adjusting factor to waves III and V latency in ABR, (p=0.044 and p=0.02, respectively). Mean of SRT test was defective in AT patients with higher clinical score of severity (p=0.02).

Delay in diagnosis of HIgM (p=0.04) and SIgAD (p=0.038) were the most important factors in otological complications of these types of PAD. Patients with early onset of HIgM had significantly higher SRT thresholds (p=0.01).

DISCUSSION

Recurrent and severe infections are hallmark of PAD due to the defect in the production of antigen specific antibodies.[24] Recurrent infectious problems of the middle ear are quite common in PAD patients.[3] However, there was lack of complementary study on otologic manifestations among these patients. This is the first study that conducts the comprehensive audiologic tests to confirm the characteristics of CHL and SNHL problems for PAD patients. Based on the findings of this study 54% of patients had otologic evidences for ENT complication specially by CHL pattern (73%). Moreover the result of the current study indicated the role of diagnostic delay and the course of disease on the presence of audiologic complication. Prior to this study, most of patients had been commenced on regular IVIg replacement therapy. Whereas, IVIg is the principal management of PAD, however, in spite of this; some patients continue to develop recurrent infections especially in mucosal surfaces, due to failure of this treatment to replace secretory IgA at these surfaces. Nonetheless, there are a few data to evaluate the late complications of recurrent ENT infections and its permanent outcomes such as hearing loss that could affect patient's quality of life. Despite the confirmed role of IVIg for PAD patients in reduction of their ENT complications, the results of current survey showed the direct association of prophylactic antibiotic therapy in control of CHL complications of CVID patients and OME in XLA individuals.

Although it is shown that bacteriologic toxins in the middle ear can damage inner ear, specifically cochlea, SNHL was not common in our patient group. This is in contrary to Berlucchi et al work.[18] This may be due to lower age of our patients at the time of diagnosis. As table 1 shows our PAD patients are diagnosed in the middle of the first decade of their life and after then they have quite less episodes of ear infections. Therefore, toxins in the middle ear do not seem to have enough time to do harm against cochlea. This also emphasizes on the importance of early diagnosis and good management of PAD patients.[18,25]

PAD patients are exposed to higher doses of antibiotics in comparison to the general population. The important point is keeping in mind the side effects of these drugs on ear and especially on cochlea.

Repeated doses of ototoxic antibiotics with the background of recurrent or chronic otitis media can lead to significant and irreversible hearing problem.[14] Mixed hearing loss in one of our CVID patient under the aminoglycoside antibiotic therapy may show such an effect.

As our data show, absolute ABR wave latencies are increased in some patients while inter-peak latency remains in normal range. This is congruent with ABR findings in ears with CHL and middle ear problem.[26]

Special characteristic of ENT problems were observed in CVID, XLA and other types of PAD in our study. These findings indicate different aspects and susceptibility for otologic complications in each type of PAD according to the nature of the disease. CVID patients showed the most frequent complication especially CHL association with more severe scoring of disease, early onset and lymphoprolifrative disorders. In contrast XLA patients showed better audiologic condition after starting IVIg and this management should be begin as earlier in these cases to prevent COM.

We had some patients with significant ear pathology in otologic investigations with negative history of ENT complaints. This emphasizes the importance of screening of asymptomatic PAD patients in this regard. Most of future complications and hearing loss can be managed by early medical or surgical intervention. A simple perforation of tympanic membrane with no ossicular chain damage that can be easily treated by a myringoplasty can be converted to massive mucosal problem and ossicular erosion by repeated infection episodes[27, 28]. In addition, due to the role of opsonin antibodies for clearing the encapsulated bacterial pathogens, hence, routine immunologic evaluation is frequently recommended in patients with a history of recurrent ENT infections at least at each 3 months.[29] Our data show a significant frequency of ear problems in PAD patients. This emphasizes the necessity for systematic complete audiologic and otologic screening and follows up of these patients. Middle ear sequel of recurrent infections such as middle ear effusions, tympanic membrane perforation, and tympanosclerosis are the most common findings. However, middle ear problems should not prevent the caring physician from possible inner ear pathology.

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