CANDIDA INFECTIONS IN ENT*

(Received 4 January, 1994)

B. Ener, M.D.**

** *Associate Professor, Department of Microbiology, Faculty of Medicine, Marmara University, Istanbul, Turkey.*

SUMMARY

Diseases caused by Candida and other fungal species are seen more frequently in recent years due to close association between their opportunistic nature and increasing number of immunocompromised and intensive care patients. Either developed surgical and medical procedures for head and neck malignancies which may cause immunosuppresion, or invasion of ENT organs during systemic infections in immunocompromised patients may be seen. New diagnostic and therapeutic modalities and approaches to such patients considering pathogenesis of candida infections were reviewed, so as to bring the clinician's site of view to the balance between the immune condition of the host and virulence of the opportunistic fungi.

Key Words: Candida infections, virulence, immunosuppression

INTRODUCTION

Fungi are very common in our environment, but only a few of them are considered true pathogens for human being, such as Histoplasma capsulatum, Coccidioides immitis, Paraccocidioides brasiliensis, Blastomyces dermatitidis. These true pathogens do not distribute world wide and their importance depends on geography. Contrary to true pathogens, most of the other fungi may cause systemic infections in certain circumstances which are mostly difficult to diagnose and cure. They are called opportunistic fungi. Because of the developing therapeutic modalities which cause immunosuppression, longer life with increasing degenerative diseases, more invasive procedures, implantation and transplantation surgery, expanded use of broad spectrum antibiotics, irradiation and acquired immune deficiency syndrome (AIDS) the incidence of mycotic infections has increased and has become more important.

Although, among opportunistic fungi, Candida species (most notably C. albicans) are the major pathogens, Aspergillus species, Cryptococcus neoformans, Fusarium species, dematiaceous (darkly pigmented) fungi, and other nonpathogenic fungi are being reported with increasing frequency. Preliminary data from the National Nosocomial Infections Surveillance System conducted by the Centers for Disease Control (Atlanta, USA) have indicated that Candida species accounted for 72% of all nosocomial fungal infections in the US over the past decade (1).

PATHOGENESIS

Numerous studies have identified host risk factors that predispose patients to opportunistic fungal infections (Table I). Evidence for the role of neutrophil activity as a main defense against systemic Candida infection has been supported by the significant incidence of disseminated infection during granulocytopenia in patients with hematologic malignancies. On the other hand the importance of the T cells in preventing mucocutaneous candidiasis has been shown by the development of chronic infections in patients with AIDS. In patients with indwelling catheters, because of alterations in cutaneous or mucosal barriers which provide portal entry, the incidence of infection increases (2-10).

Apart from predisposing factors, the microorganism must possess specific factors or mechanisms of pathogenesis that enables them to cause infection. Specific factors associated with the ability of the fungus to cause infection are shown in table II. Adherence is the first step to establish colonization and infection. C. albicans is known to colonize humans more frequently than the other fungi (11,12). Variations among strains of C. albicans to adhere epithelial cells have been demonstrated, and in some studies a close correlation was observed between the adherence ability of a strain and virulence (13-15). Relevant factors that enhance adherence include fungal cell surface hydrophobicity (CSH), enviromental factors, phenotype of the organism, pH, and temperature. CSH enhances candidal adherence to epithelial cells and the virulence increases due to the ability of hydrophobic cells to bind host tissue (15-17). Production of extracellular hydrolytic enzymes has been demonstrated in some strains of C. albicans. A few of them have been found associated with pathogenesis, including acid phosphomonoesterase (18). phospholipase (19-22) and acid protease (23-26). Isolates with greater in vitro enzyme activity are usually more virulent.

There are very few studies that investigate correlation between pathogenicity and multiple virulence factors. Barrett-Bee et al. (19) refined assays for the detection of extracellular and intracellular phospholipase A and lysophospholyase and compared the activities of these enzymes with the ability of an isolate to adhere

* *This article was presented at the "XV. World Congress of Otorhinolaryngology Head and Neck Surgery, Istanbul, Turkey," on 25 June, 1993.*

and to be pathogenic for mice. Ghannoum and Elteen (23) examined proteinase activity, and adherence to buccal epithelial cells, and pathogenecity for mice. In these studies, it was found that isolates that were more lethal to mice tended to have elevated enzyme activity and enhanced adherence abilities compared with less lethal isolates. We compared cell surface hydrophobicity, adherence and phospholipase activity of 35 C. albicans strains isolated from a group of patients either immunocompromised or immunocompetent (27). Our initial results revealed that if the patient had important predisposing factor, isolated Candida strains had been found to be either high or low virulent, but the patients who had relatively less predisposing factor such as antibiotic use, disease causing isolates were significantly more virulent, while the isolates only colonizing but not causing infection had lower virulence factors. According to these findings, virulence factors should be more important for the patient who has relatively competent immunity. Determination of virulence factors may help to identify the risk of invasion and dissemination. On the other hand isolation of a low virulent strain from a patient with invasive candidiasis may call suspicion of any defect in immune defence. Further studies with more isolates are necessary to support these findings. At present no invitro system based on virulence factors of C. albicans can accurately predict the pathogenic potential of an isolate. However, if a panel of standardized method is developed to assess these factors quantitatively, perhaps pathogenic potential of a strain can be predicted according to its characteristics determined in a clinical laboratory.

CLINICAL FEATURES AND THERAPEUTIC APPROACH

Actually mycotic disease is a very limited subject in ENT which has a broad spectrum in many ways. Fungal infections related to ENT can be divided into two subgroups because of their considerably different clinical features, therapeutic approach and outcomes:
1- Local fungal infections like otitis externa, otitis media, sinusitis in relatively immunocompetent patients

Table I- Predisposing factors for opportunistic fungal infections

- Deficient neutrophil number or function *
- Deficient T cell number or function
- Deficient macrophage and monocyte number or function
- Antibiotic therapy *
- Corticosteroid therapy
- Immunosuppressive therapy
- Intravascular catheters *
- Parenteral hyperalimantation
- Extensive surgery
- Prior colonization by fungal species *
- Malnutrition
- Hyperglisemia and asidosis
- Ulcerations of the oropharyngeal or gastrointestinal mucosa

* Independent risk factors for candidemia (1,7 - 9)

Table II- Virulence properties of Candida species

- Cell surface hydrophobicity
- Adherence to host cells or artificiale surfaces
- Yeast receptors that bind a complement component
- Hydrolytic enzymes (Proteinases, phospholipases, lysophospholipases)
- Dimorphism and phenotypic switching

2- Local or systemic infections in immunocompromised patients
Fungal otitis externa is usually seen as a superficial, subacute or chronic disease of the external auditory canal and most frequently encountered pathogens are Candida and Aspergillus species (28-30). The ratio of fungi isolated from symptomatic patients with otitis externa varies between 50% and 100% in different studies (28,30-32). Most of fungi are *Aspergillus* species and *Candida* species (10-20%). It was also found that fungi could be isolated in the external auditory canal with a ratio of about 11-15% in completely normal persons(33). So, fungi can be

isolated as normal flora in many patients without infection, can be isolated together with bacterial agents in mixed otitic infection or can be isolated from pure fungal infections. Therefore one should be very careful in deciding if the isolated fungi are the causative agents or not; because these fungi can be found at the external auditory canal especially in moist and warm environment. If the patient has any debilitating factor, if there are improper hygenic conditions, and if there is no cure with antibacterial therapy, suspicion should be directed to mycotic infections.

Mycotic infections of middle ear, mastoid, and sinuses have rarely been reported. Apart from allergic fungal sinusitis which is caused especially by Aspergillus species and dematiaceous fungi (34-36) and mucormycosis that are associated with diabetic ketoacidosis (37), most of the cases are seen in immunosuppressed patients. During systemic candidiasis very rare involvement of middle ear, temporal bone, and sinuses is surprising. Candida infections of oropharyngeal, gastrointestinal, and genitourinary tracts have been known to occur even in normal children who are treated with multiple antibiotics but invasion of middle ear, mastoid and sinuses is seldom (38-40). Several reports emphasize that mycotic infection of the auditory canal, middle ear, and sinuses occurred in patients who were at high risk because of extensive operations, immunosupression, long-term antibiotic therapy or organ transplantation (39,41).

Oral, pharyngeal, laryngeal and esophageal infections caused by Candida species are problematic in clinics and occur very frequently in immunocompromised patients. Immunocompromise can result from trauma, burns, cancer especially hematologic malignancies, cancer chemotherapy, irradiation, and immunosupressive therapy. Beacuse of the need for interruption of therapeutic radiation in patients with head and neck cancer and risk of dysfunction of the voice prosthesis, oropharyngeal colonization and infection of Candida species and therapeutic approaches gain more importance nowadays (42). Additionally the most frightening problem in these immunocompromised patients is the invasive and systemic fungal infections. It is reported that Candida species are found in about 30% of immunosuppressive patients who died of infection (43). Difficult and time-consuming diagnosis and troubles in the treatment result with high mortality rates. Because the conventional laboratory diagnostic techniques are time-consuming, new sero-diagnostic techniques are under investigation. Although the sensitivity and specificity of these techniques have not been found satisfactory until now, they may play some role in diagnosis (44,45). Many reports emphasize that early therapeutic intervention whether surgical, or medical, or both significantly diminishes mortality. In many institutions, in cases of fever that do not respond to antibacterial therapy in 5-7 days, empiric antimycotic therapy is preferred and recommended (46).
Although there are not many resistant species to amphotericin B so far, the toxic effect has limited its use and has prompted investigations for the new less toxic agents. Liposomal amphotericin B and imidazole derivates such as ketoconazole, fluconazole and itraconazole are already in clinical use (46). Clinical studies show that fluconazole is very effective against Candida albicans. Because of its low toxicity compared with amphotericin B, it is preferred for antimycotic prophylaxis in immunocompromised patients. It is also recommeded for neutropenic patients. (47,48). But it is reported that in spite of antimycotic chemoprophylaxis in some patients, Candida infections caused by Candida species other than C. albicans and Aspergillus spp. may occur (49). Debates on the therapeutic and prophylactic doses of antimycotics are still going on. Because of such observations and unreliability of invitro susceptibility tests, amphotericin B should be the drug of choice in life-threatening cases.

CONCLUSION

Fungi as causative agents of infections should always be kept in mind.

The patient should be examined as a whole, and, each and every predisposing factor for a mycotic infection should be determined.

Early suspicion of mycotic infection and early therapeutic intervention may diminish mortality and morbidity.

Most serious fungal infections occur in a setting of impaired host defence mechanism and resolution of these deficiencies may be more important in the control of the infection than administration of antifungal chemotherapy.

REFERENCES

1. *Pfaller MA. Epidemiological typing methods for mycoses. Clin Infect Dis 1992;14(suppl1):4-10.*
2. *Quentzel MN, Cole GT, Pope LM. Animal models for candidiasis. In: McGinnis MR, ed. Current topics in medical mycology, vol 1. New York: Springer Verlag, 1985:57-70.*
3. *Anaissie E, Bodey GP, Kantarjian H, et al. New spectrum of fungal infections in patients with cancer. Rev Infect Dis 1989;11:369-378.*
4. *Meunier F. Prevention of mycoses in immunocomprimised patients. Rev Infect Dis 1987;9:408-416.*
5. *Odds FC. Candida infections: an overview. CRC Crit Rev Microbiol 1987;15:1-5.*
6. *Miller PJ. Wenzel RP. Etiologic organisms as independent predictors of death and morbidity associated with bloodstream infections. J Infect Dis. 1987;156:471-477.*
7. *Bross J, Talbot GH, Marslin G, Hurwitz S, Strom BL. Risk factors for nosocomial candidemia: a case control study in adults without leukemia. Am J Med 1989;87:614-620.*
8. *Schwartz RS, Mackintosh FR, Schrier SL, Greenberg PL. Multivariate analysis of factors associated with invasive fungal disease during remission-induction therapy for acute myelogenous leukemia. Cancer 1984;53:411-419.*
9. *Karabinis A, Hill C, Leclercq B, Tancrede C, Baume D, Andremont A. Risk factors for candidemia in cancer patients: a case control study. J Clin Microbiol 1988;26:429-432.*

10. Komshian SV, Uwaydah AK, Sobel JD, Crane LR. Fungemia caused by candida species and Torulapsis glabrata in the hospitalized patient: frequency, characteristics, and evaluation of factors influencing outcome. Rev Infect Dis 1987;1:379-390.
11. Douglas LJ. Adhesion of Candida species to epithelial surface. CRC Crit Rev Microbiol 1987;15:2-16.
12. Douglas LJ. Adhesion to surfaces. In: Rose AH, Harrison JS, eds. The yeasts, Vol 2. London, Academic Press Inc, 1987:239-275.
13. Kearns MJ, Davies P, Smith H. Variability of the adherence of Candida albicans strains related to virulence. Sabouraudia 1984;2:93-98.
14. McCourtie J, Douglas LJ. Relationship between cell surface composition, adherence, and virulence of Candida albicans. Infect Immun 1984;45:6-12.
15. Ener B, Douglas LJ. Correlation between cell surface hydrophobicity of Candida albicans and adhesion to buccal epithelial cells. FEMS Microbiol Lett 1992;99:37-42.
16. Hazen KC, Lay LC, Hazen BW, Fu RC, Murthy S. Partial biochemical characterization of cell surface hydrophobicity and hydrophilicity of Candida albicans. Infect Immun 1990;58:3469-3476.
17. Hazen KC, Brawner DL, Riesselman MH, Jutila MA, Cutler JE. Differential adherence of hydrophobic and hydrophilic Candida albicans yeast cells to mouse tissue. Infect Immun 1991;59:907-910.
18. Odds FC, Hierholzecr JC. Purification and properties of a gycoprotein acid phosphatase from Candida albicans. J. Bacteriol 1973;114:257-266.
19. Barrett-Bee K, Hayes Y, Wilson RG, Rilay F. A comparison of phopholipase activity, cellular adherence and pathogenicity of yeast. J Gen Microbiol 1985;131:1217-1221.
20. Price MF, Wilkinson ID, Gentry LO. Plate method for detection of phospholipase in Candida albicans. Sabouraudia 1982;20:7-14.
21. Williamson MI, Samaranayaka LP, MacFarlane TW. Phopholipase activity as a criterion for biotyping Candida albicans. J Med Vet Mycol 1986;24:415-417.
22. Ener B, Babacan F, Johansson CB. In vitro detection of phopholipase activity in Candida species. Med Bull 1991;24:55-60.
23. Ghannoum MA, Elteen KA. Correlative relationship between proteinase production, adherence and pathogenecity of various strains of Candida albicans. J Med Vet Mycol 1986;24:407-413.
24. Kwan-Chung KJ, Lehman D, Good C, Magee PT. Genetic evidence for role of extracellular proteinase in virulence of Candida albicans. Infect Immun 1985;49:571-575.
25. MacDonald F. Secretion of inducible proteinase by pathogenic Candida species. J Med Vet Mycol 1984;22:79-82.
26. Ruchel R, Tegelar R, Trost M. A comparison of secretory proteinase from different strains of Candida albicans. Sabouraudia 1982;20:233-244.
27. Ener B, Gülen D, Ülger N, Johansson CB. Comparison of various virulence factors of Candida albicans isolated from clinical specimens. 4th National Infectious Disease Congress Abstract Book, April 27-30 izmir-Türkiye, 1993;158.
28. Paulose KO, Al Khalifa S, Shenoy P, Sharma RK. Mycotic infection of the ear (otomycosis): A prospective study. J Laryngol Otol 1989;103:30-33.
29. Stern JC, Lucenk FE. Otomycosis. Ear Nose Throat J (USA). 1988;67:804-807.
30. Yehia MM, Al Habib HM, Shehabin NM. Otomycosis: A common problem in North Iraq. J Laryngol Otol 1990;104:387-389.
31. Hawke M, Wong J, Krajden S. Clinical and microbiological features of otitis externa. J Otolaryngol 1984;13:289-292.
32. Durmaz B, Durmaz R, Erpek G, Özcan A. Fungi encountered in cases of otomycosis. Turkish J Infect 1991;5:131-133.
33. Coşkuner Ş. Investigation on the flora of external auditory meatus. J Turk Microbiol Soc 1971;1(3-4):220-227.
34. Killingsworth SM, Wetmore SJ. Curvularia/ Drechslera Sinusitis. Laryngoscope 1990;100:932-937.
35. Allphin AL, Strauss M, Abdul-Karim W. Allergic fungal sinusitis: Problems in diagnosis and treatment. Laryngoscope 1991;101:815-820.
36. Manning SC, Schafer SD, Close LG, Vuitch F. Culture positive allergic fungal sinusitis. Arch Oto Laryngol Head Neck Surg 1991;117:174-178.
37. Anand VK, Aleiner G, Griswol JA. Intracranial complications of mucormycosis: An experimental model and clinical review. Laryngoscope 1992;102:656-662.
38. Keller MA, Sellers BB, Melish ME, Kaplan GW, Miller KE, Mendoza SA. Systemic candidiasis in infants. Am J Dis Child 1977;131:1260-1263.
39. Cohen SR, Thompson JW. Otitis candidiasis in children: An evalution of the problem and effectiveness of ketoconazole in 10 patients. Ann Otol Rhinol Laryngol 1990;99:427-431.
40. Chelidze N. Otomycosis in childhood. Vestn Otorinolaringol 1983;1:22-26.
41. Falser N. Fungal infection of the ear: Etiology and thearpy with bifonazole cream or solution. Dermatologica 1984;169:135-140.
42. Mahieu HF, Van Saene JM, Den Besten J, Van Saene HKF. Oropharynx decontamination preventing Candida vegetation on voice prostheses. Arch Otolaryngol Head Neck Surg 1986;112:1090-1092.
43. Anaissie E. Oportunistic mycoses in the immunocompromised host: Experience at a cancer center and review. Clin Infect Dis. 1992;14 (suppl 1): 43-53.
44. De Repentigny L. Serodiagnosis of candidiasis, aspergilosis, and cryptococcosis. Clin Infect Dis 1992;14 (suppl 1):11-22.
45. Kaufman L. Laboratory methods for the diagnosis and confirmation of systemic mycoses. Clin Infect Dis 1992;14 (supp 1): 23-29.
46. Walsh TJ, Lee J, Lecciones J et al. Empiric thearpy with amphotericin B in febrile granulocytopenic patients. Rev Infect Dis 1991; 13:496-503.
47. Bucher T Roos N. Antifungal treatment strategy in leukemia patients. Ann Hematol 1992;65:153-161.
48. Walsh TJ, Lee JW, Roilides E, Francis P, Bacher J, Lyman CA, Pizzo PA. Experimental antifungal chemotherapy in granulocytopenic animal models of disseminated candidiasis: approaches to understanding investigational antifungal compounds for patients with neoplastic diseases. Clin Infect Dis 1992;14 (supp 1):139-147.
49. Meis JF, Donnely JP, Hoogkamp-korstanje JA, DePauw BE. Aspergillus fumigatus pneumonia in neutropenic patients during therapy with fluconazole for infection due to Candida species. Clin Infect Dis 1993;16:734-735.

Erratum

1. The photographs on page 75 and 76 in Volume 7, No 2, April 1994 should be replaced with the following photographs.

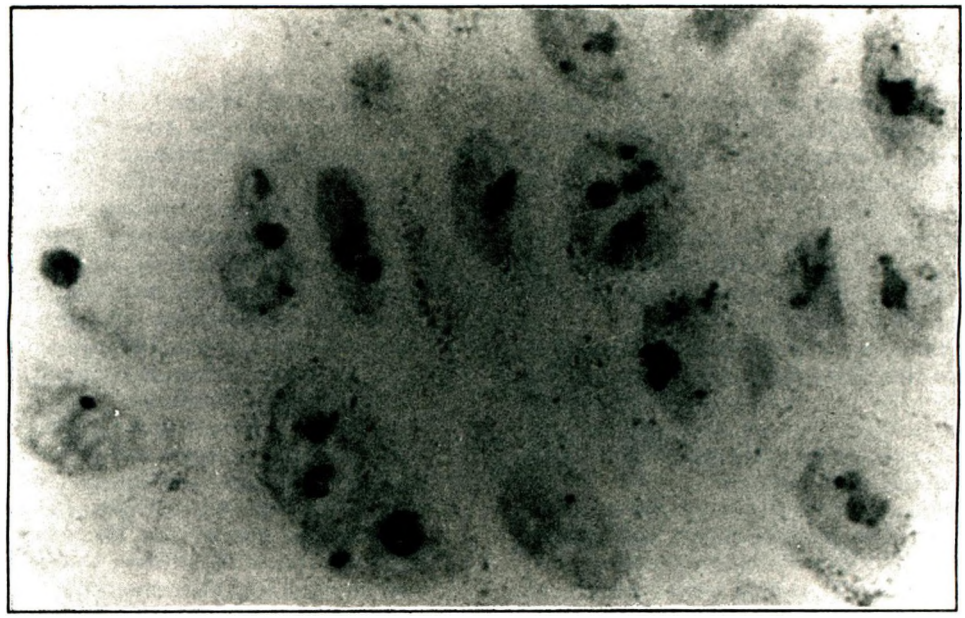

Fig. 1: AgNORs staining of squamous cell carcinoma of the vocal cords.

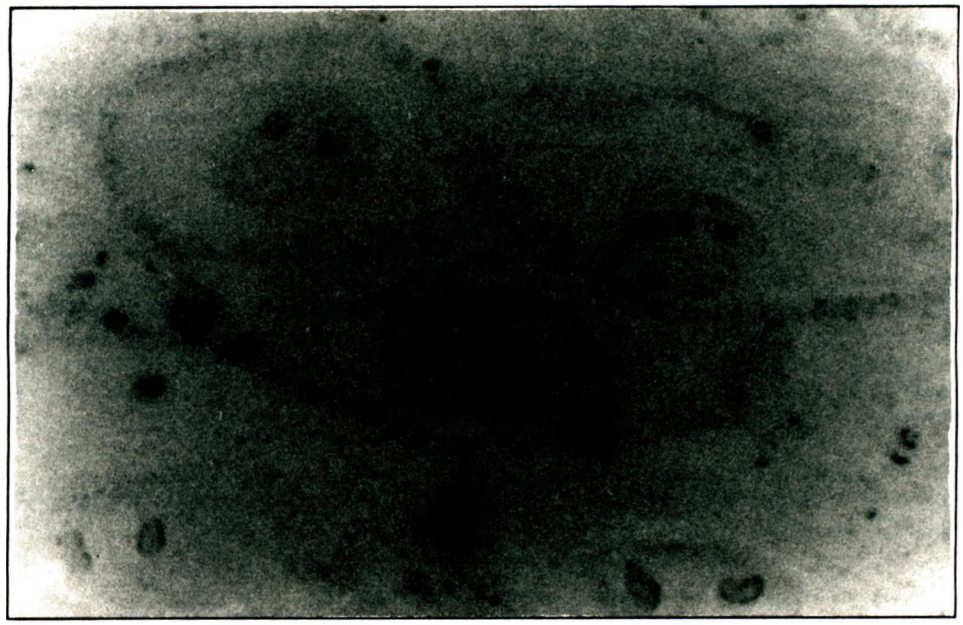

Fig. 2: AgNORs staining of dysplasia of the vocal cords

2. The date on page 64 in Volume 7, No 2, April 1994 should be (Received 27 September 1993) not (Received 27 September, 1994) as stated.

MARMARA MEDICAL JOURNAL
INSTRUCTIONS TO AUTHORS

1. Manuscripts, letters and editorial correspondence should be sent to "Editor, Marmara Medical Journal, Marmara University, Faculty of Medicine, Istanbul-Turkey" by first class mail (airmail for overseas).
2. Submissions considered for publication are received with the understanding that no part of the submission has previously appeared elsewhere in any but abstract form.
3. Manuscripts should be typed double-spaced on standard size typewriter paper with margins of at least 2.5 cm. This includes references, tables and figure-legends. The original typescript and two high-quality copies of the manuscripts should be submitted.
4. Number pages consecutively in order and place author (s) name, highest degree, institutional affiliations and address below the title.
5. Marmara Medical Journal invites papers on original research, case reports, reviews, short communications for practical applications, letters, editorials, book reviews and announcements. The number of typewritten pages should not exceed 10 for original articles, 12 for reviews, 4 for case reports and 1 for letters.
6. Original articles and research papers should normally be divided into following sections: A. (1) An informative summary for not more than 200 words must be included and should appear at the beginning of the paper. (2) Key words. (3) Introduction. (4) Materials and Methods. (5) Results. (6) Discussion,and (7) References.

   B. References must be typed in double spacing and numbered consecutively as they are cited. The style of references is that of the Index Medicus. List all authors when there are six or fewer, when there are seven or more, list the first three, then "et al". Sample references follow:

   1. Steward JH, Castaldi PA. Uremic bleeding: a reversible platelet defect corrected by dialysis. QJ Med. 1967; 36 : 409 - 23.

   2. Bearn AG. Wilson's Disease. In: Stanbury JB, Wyngaarden JB, Fredrickson DS, eds. The metabolic basic of inherited disease. New York : McGraw - Hill, 1972: 103-50.
7. Tables should be as few as possible and should include only essential data. Tables should be typed in double spacing on separate sheets and have a legend for each. Diagrams or illustrations should be drawn with black Indian ink on white paper and should be given Roman numerals. Each illustration should be accompanied by a legend clearly describing it - all legends should be grouped and typewritten (double spaced) on a separate sheet of paper. Photographs and photomicrographs should be unmounted high contrast glossy black on white prints and should not be retouched. Each photograph or illustration should be marked on the back with the name (s) of the author (s), should bear on indication of sequence number and the top should be marked with an arrow. All measurements should be given in metric units.
8. Manuscripts are examined by the editorial board usually sent to out side referees. The editor reserves the right to reject or to return the manuscript to the author(s) for additional changes if all the guidelines and requirements are not uniformly completed. Only two copies of the rejected papers are returned to the author (s).
9. Proofs will be submitted to the author responsible for proof correction and should be returned to the editor within 5 days. Major alterations from the text cannot be accepted.
10. Correspondence and communications regarding manuscripts and editorial material subscriptions and payments should be sent to:

    The Editor
    Marmara Medical Journal
    Marmara University, Faculty of Medicine
    Haydarpaşa - Istanbul.