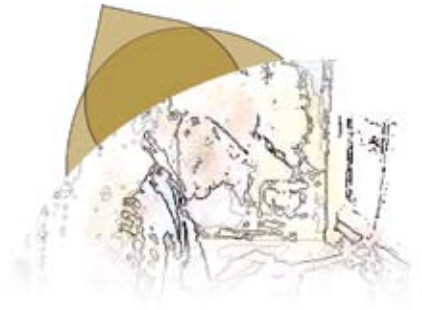


Middle East Journal of Age and Ageing
ISSN 148-4196 June 2007 Volume 4 Issue 3

Contents

Volume 4, Issue 3
June 2007

Editorial

Author
Dr Abdulrazak Abyad
Chief editor

In this issue of the journal the papers are each from different parts of the world. A review paper from the UK discusses the use of drugs in older people. The authors stressed that as people age they develop diseases and this leads to more prescribing – both to prevent disease progression and for symptomatic relief. The authors discussed "appropriate prescribing" a term that has been introduced to describe a strategy which tries to ensure that all older people receive only medications which are beneficial whilst at the same time potentially harmful drugs are avoided.

A research paper from Egypt and Japan investigated the detection accuracy of head and neck cancer and lymph node metastasis by FDG-PET compared with CT and MRI, and to validate the results with the histopathological data. The authors concluded that compared with CT and MRI, FDG-PET was found to have the same sensitivity for primary cancer/recurrence detection, however, it was the most sensitive modality for detection of lymph node metastasis. Moreover, the whole-body FDG-PET imaging proves auseful tool for detection of distant metastasis and synchronous tumours.

A paper from Pakistan reviewed psychological issues of older women. The authors stressed that in our part of the world, social attitudes as well as cultural practices (Karo Kari, exchange marriages, dowry, etc.), play a vital role in women's mental health. Female status in Pakistan and the consequential effects on their mental health, finds a marked diversity in the lives of the urban and rural women, be it their identity, self-image, political awareness, freedom of expression or social status. It has been observed that women in Pakistan are physically battered and their men mentally and verbally abuse them. The author pointed out as well that factors positively associated with anxiety and depressive disorders in women of Peshawar were mainly due to social problems, and cultural taboos.

A paper from Iran discussed the status of charitable health organisations in some Islamic countries. The authors emphasised that charitable work fills critical gaps in the global socio-economic infrastructure. Governmental organizations alone cannot solve every social problem. Without international charity , more people in the world would die of hunger , disease and live in poverty . The author points out that in Kuwait, International Islamic charitable organization (IICO) has branches and offices all over the state. Their strategy is to present an Islamic model of integrated modern charitable work. More than sixty countries around the world are benefiting from IICO charitable work. The author concluded that considering the successful pattern and strong points of the charities in other countries, they need help to promote the status of charity service delivery to the community.

Another combined paper from Lebanon and Canada attempted to identify the genetic cause of early onset Parkinson's disease (PD) in a large consanguineous Lebanese family affected with the disorder. The authors report that haplotype analysis of the recessive PD loci suggested a PARK2 involvement in this family. Mutation analysis of the PARK2 gene revealed a homozygous deletion of a guanine at the end of exon 9 (1081delG), which leads to the predicted introduction of a premature stop codon. They concluded that a novel causative mutation in PARK2 was identified in a consanguineous Lebanese family, which could potentially lead to the development of a PD diagnostic tool for the Lebanese population.

A Case report from Ireland discussed a case of hypothyroidism in an elderly woman. The authors reported a case of an elderly lady who presented with severe dementia (mini-mental score of 8/30), with dramatic improvement, following replacement of thyroid hormone. Mini-mental score of 30/30 on discharge. This case showed clearly the importance of hypothyroid screening in the elderly.

A paper from California discussed independent grandmothers in an Iranian village

The author presented a model from "Aliabad," a large village in south-western Iran, where older widowed women are often deciding to live by themselves in their own homes rather than living with sons as was generally the case until recently. The author presented their research data collected in Aliabad, interview and participant observation in other nearby villages and Shiraz, and extensive fieldwork among Iranian grandparents in California's Santa Clara Valley.

Original Contribution/Clinical Investigation

A PARK2 Mutation In A Consanguineous Lebanese Family Affected with Early-onset Parkinson Disease

Author:
Dominique J. Verlaan Ph.D.[1,2], Tadeu Fantaneanu B.Sc.[1], Inge A. Meijer Ph.D.[1], Daniel L. Rochefort M.Sc.[1], Mélanie Bénard B.A.[1], Rosette Jabbour M.D.[3], Guy A. Rouleau M.D., Ph.D.[1]
1Faculte de Medecine, Universite de Montreal, Centre de recherche du CHUM, Hopital Notre-Dame-CHUM, Montreal, Quebec, Canada.
2Department of Human Genetics, McGill University, Montreal, Quebec, Canada.
3 Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon.

Correspondence:
Dr. Guy A. Rouleau,
Centre de recherche du CHUM,
Hôpital Notre-Dame,
1560 rue Sherbrooke Est,
Bureau Y-3633, Montréal,
Québec H2L 4M1,
Canada

ABSTRACT

Aim: To identify the genetic cause of early onset Parkinson's disease (PD) in a large consanguineous Lebanese family affected with the disorder.
Methods: Genotyping of polymorphic microsatellites at the three recessive PD loci (PARK2, PARK6 and PARK7) was performed on the family, followed by direct sequencing of the PARK2 gene.
Results: Haplotype analysis of the recessive PD loci suggested a PARK2 involvement in this family. Mutation analysis of the PARK2 gene revealed a homozygous deletion of a guanine at the end of exon 9 (1081delG), which leads to the predicted introduction of a premature stop codon.
Conclusion: A novel causative mutation in PARK2 was identified in a consanguineous Lebanese family, which could potentially lead to the development of a PD diagnostic tool for the Lebanese population.

Key Words: Parkinson disease; PD; mutation; PARK2; neurodegenerative.

Introduction

Parkinson disease (PD; MIM# 168600) is a prevalent age-associated progressive neurodegenerative disorder first described by James Parkinson in 1817. After Alzheimer's disease, it is the second most common neurodegenerative disorder, affecting 2% of the population who are over the age of 65[1]. It is characterized by a combination of resting tremor, bradykinesia and rigidity and postural instability. Other features may include dementia, dystonic cramps and dysautonomia. Idiopathic PD onset usually occurs in mid to late adulthood. Patients frequently have an excellent initial symptomatic response to levodopa therapy; however, it does not slow PD progression and it may also provoke undesirable side effects, such as dyskinesia[2,3]. Pathologically, there is a loss of dopaminergic neurons in the substantia nigra (SN)4. In addition, Lewy bodies, which are intracellular inclusions, are present in the surviving neurons mainly in the SN but also in other areas of the brain[4].

The aetiology of the disease is still largely unknown, but genetic susceptibility factors in some families are strongly suspected. To date, seven autosomal dominant loci including mutations in four genes have been identified: PARK1/PARK4 on chromosome 4q21 (SNCA gene)[5], PARK3 on 2p13[6], PARK5 on 4p14 (UCHL1 gene)[7], PARK8 on 12q12 (LRRK2 gene)[8], PARK10 on 1p9, PARK11 on 2q[10] and PARK13 on 2p12 (HTRA2 gene)[11]. Three autosomal recessive loci and their respective genes have also been described: PARK2 on chromosome 6q25.2-q17 (PARK2 gene)[12], PARK6 on 1p36 (PINK1 gene)[13] and PARK7 on 1p36 (DJ1 gene)[14].

We identified a large consanguineous Lebanese family affected with adult onset Parkinson's disease. The family

consists of three sisters who became affected with PD in their late twenties and that have the classical triad of features of bradykinesia, rigidity, and tremor **(Table 1 and Figure 1)**. The sisters responded very well to levodopa therapy. The unaffected parents are 1st degree cousins and for this reason, loci that are known to cause recessive PD - PARK2, PARK6 and PARK7 - were first investigated by genotyping.

Table 1: Clinical information

Patient	Age	Age of onset	Tremor	Cogwheeling	Akinesia	Postural deficit	Dyskinesia
II:3	47	30	Y	N	Y	Y	Y
II:7	41	27	Y	Y	Y	N	Y
II:10	34	27	Y	Y	Y	Y	N

Y: yes, N: no

Materials and Methods

Patients: Informed consent was obtained from all patients and family members. Blood samples were collected from each subject and DNA was extracted from peripheral blood by standard methods. Clinically, the three affected subjects were first investigated for Wilson's disease by testing their ceruloplasmin level, serum copper and 24-hours copper in urine, which were normal. Magnetic Resonance Imaging (MRI) of the brain was performed and was also normal.

Linkage analysis and haplotyping: Linkage was performed using polymorphic markers obtained from the Marshfield genetic map, and the primer sequences were obtained from the Genome Database and the Cooperative Human Linkage Center database. Each primer pair was amplified according to specific Polymerase Chain Reaction (PCR) conditions and was labelled by incorporating the nucleotide S35-dATP in the product. The PCR products were separated on 6% denaturing polyacrylamide gels and detected by exposure to autoradiographic film. The alleles were assigned on the basis of their size, with comparison to a M13mp18 sequence ladder. Marker location was obtained from the UCSC physical map (March 2006 Assembly, NCBI build 36.1). D6S1579, D6S1550, D6S305, D6S1599 and D6S1277 were analyzed for the PARK2 locus; D1S2694, D1S548 and D1S1612 were analyzed for the PARK6 locus; and D1S199, D1S3720, D1S2864, D1S482 and D1S2674 were analyzed for the PARK7 locus.

Gene analysis: Each of the 12 PARK2 exons was amplified by PCR with intronic primers and was sequenced on an ABI3700 automated sequencer using BigDye chemistry, according to the manufacturer's recommended protocol (Applied Biosystems, Foster City, CA).

Results

Haplotype analysis showed that there was no segregation of the disease with a haplotype at the PARK6 and PARK7 loci (data not shown). In contrast, all affected individuals were homozygous for the same haplotype **(Figure 1)** at the PARK2 locus. In addition, all of the normal individuals were heterozygous for the disease haplotype or did not carry it at all. A haplotype recombination event was found in Individual II:10, suggesting that a causative mutation would not be found in the first six exons of the PARK2 gene.

Mutation analysis of the PARK2 gene revealed a single base pair deletion of a guanine at nucleotide 1081 at the end of exon 9. This deletion was found in a homozygous state in all three affected sisters **(Figure 2)**. This mutation presumably leads to a frameshift that introduces a premature stop codon leading to a novel C-terminus containing 72 new amino acids.

Figure 1: Haplotype analysis of the consanguineous Lebanese family at the PARK2 locus. A black bar represents the disease haplotype. Parentheses represent inferred alleles Black symbol: affected; White symbol: normal.

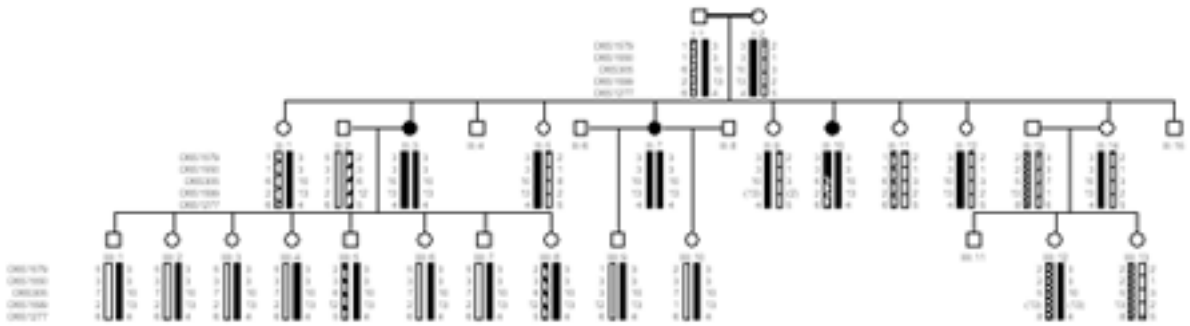
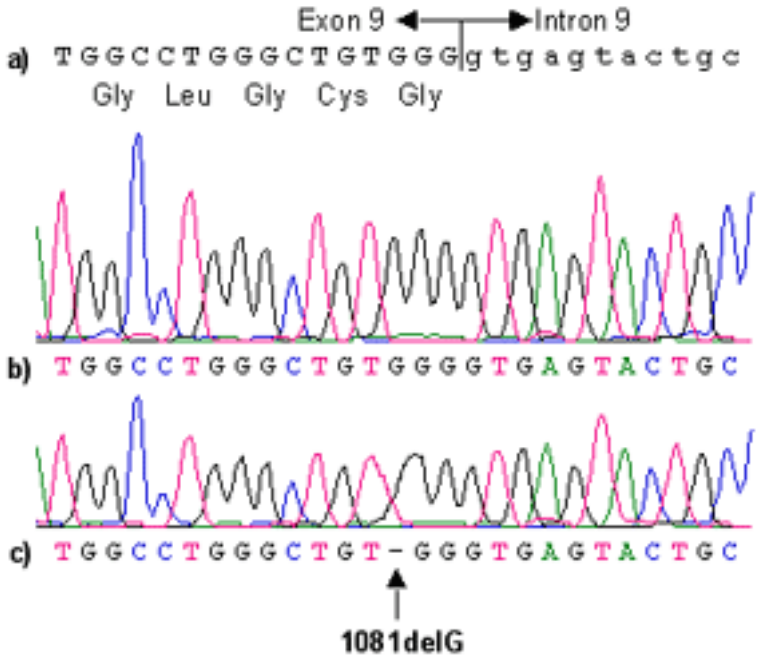


Figure 2:

a) Normal PARK2 sequence showing the junction between exon 9 and intron 9

b) Normal sequence of a control

c) Mutated sequence in a homozygous state of an affected individual with a deletion of a guanine at nucleotide 1081 (1081delG). This is a frameshift mutation, which leads to a premature stop codon.



Discussion

We have identified a consanguineous Lebanese family that is affected with early onset Parkinson Disease and which segregates a mutated PARK2. An extensive review of the literature suggests that this novel 1081delG mutation is the first PARK2 mutation described in a Lebanese family. Our results support the evidence that PARK2 mutations are very prevalent in PD and are present in nearly every ethnicity[15]. The likelihood of carrying PARK2 mutations in individuals with parkinsonism is inversely associated with age and may be as high as 50% in individuals who are younger than 25 years old[16]. Interestingly, PARK2 mutations may not only cause early-onset PD but may also be involved in later-onset PD (greater than 60 years) when individuals only have one mutated copy**17,18**.

The PARK2 gene, which is mutant in autosomal recessive juvenile parkinsonism (PDJ) (OMIM: 600116) maps to 6q26, contains 12 exons and spans 1.3Mb of genomic DNA12. PARK2, which is one of the largest genes in the human genome, lies within the hyper-recombinable fragile site FRA6E[19]. All types of mutation have been identified in the PARK2 gene: multiplications, small deletions/insertions, large genomic deletions as well as splice, missense and nonsense mutations. Most of the missense mutations occur within consensus domains of the gene and affect amino acids which are usually conserved in the mouse. The PARK2 gene encodes for a 465 amino acid protein called parkin, which includes an ubiquitin homologous domain in its N-terminus and two RING finger domains in its C-terminus. Parkin functions as an E3 ubiquitin ligase[20] and may interact with alpha-synuclein (SNCA), a protein which is also involved in PD[21]. The protein resulting from the 1081delG mutation would presumably be lacking the last RING domain and contain a disrupted IBR domain.

Lastly, it will be interesting to ascertain if this mutation can also be found in other early-onset PD Lebanese families and in patients with an older age of onset, as well as PD patients from other ethnic origins. In addition, further characterization of this mutation could potentially lead to the development of PD diagnostic and prenatal diagnostic tools for the Lebanese population.

Acknowledgements

We would like to especially thank the family for participating in this study. DJV is supported by a Quebec Health Research Fund Training and Support for Research scholarship. GAR is supported by the Canadian Institute of Health Research and the Quebec Health Research Fund.

References

1. de Rijk MC, Tzourio C, Breteler MM et al. Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON Collaborative Study. European Community Concerted Action on the Epidemiology of Parkinson's disease. J Neurol Neurosurg Psychiatry. 1997;62:10-15
2. Lang AE, Lozano AM. Parkinson's disease. First of two parts. N Engl J Med. 1998;339:1044-1053
3. Lang AE, Lozano AM. Parkinson's disease. Second of two parts. N Engl J Med. 1998;339:1130-1143
4. Braak H, Del Tredici K, Rub U et al. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003;24:197-211
5. Polymeropoulos MH, Lavedan C, Leroy E et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science. 1997;276:2045-2047
6. Gasser T, Muller-Myhsok B, Wszolek ZK et al. A susceptibility locus for Parkinson's disease maps to chromosome 2p13. Nat Genet. 1998;18:262-265
7. Leroy E, Boyer R, Auburger G et al. The ubiquitin pathway in Parkinson's disease. Nature. 1998;395:451-452
8. Paisan-Ruiz C, Jain S, Evans EW et al. Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. Neuron. 2004;44:595-600
9. Li YJ, Scott WK, Hedges DJ et al. Age at onset in two common neurodegenerative diseases is genetically controlled. Am J Hum Genet. 2002;70:985-993
10. Pankratz N, Nichols WC, Uniacke SK et al. Genome screen to identify susceptibility genes for Parkinson disease in a sample without parkin mutations. Am J Hum Genet. 2002;71:124-135
11. Strauss KM, Martins LM, Plun-Favreau H et al. Loss of function mutations in the gene encoding Omi/HtrA2 in Parkinson's disease. Hum Mol Genet. 2005;14:2099-2111
12. Kitada T, Asakawa S, Hattori N et al. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature. 1998;392:605-608
13. Valente EM, Abou-Sleiman PM, Caputo V et al. Hereditary early-onset Parkinson's disease caused by mutations in PINK1. Science. 2004;304:1158-1160
14. van Duijn CM, Dekker MC, Bonifati V et al. Park7, a novel locus for autosomal recessive early-onset parkinsonism, on chromosome 1p36. Am J Hum Genet. 2001;69:629-634
15. Jones AC, Yamamura Y, Almasy L et al. Autosomal recessive juvenile parkinsonism maps to 6q25.2-q27 in four ethnic groups: detailed genetic mapping of the linked region. Am J Hum Genet. 1998;63:80-87
16. Fahn S, Sulzer D. Neurodegeneration and neuroprotection in Parkinson disease. NeuroRx. 2004;1:139-154
17. Foroud T, Uniacke SK, Liu L et al. Heterozygosity for a mutation in the parkin gene leads to later onset Parkinson disease. Neurology. 2003;60:796-801
18. Pramstaller PP, Schlossmacher MG, Jacques TS et al. Lewy body Parkinson's disease in a large pedigree with 77 Parkin mutation carriers. Ann Neurol. 2005;58:411-422
19. West AB, Maidment NT. Genetics of parkin-linked disease. Hum Genet. 2004;114:327-336
20. Shimura H, Hattori N, Kubo S et al. Familial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase. Nat Genet. 2000;25:302-305
21. Shimura H, Schlossmacher MG, Hattori N et al. Ubiquitination of a new form of alpha-synuclein by parkin from human brain: implications for Parkinson's disease. Science. 2001;293:263-269

Original Contribution/Clinical Investigation

Head and Neck Cancer with Lymph Node Metastasis: Comparison at CT, MRI, FDG-PET and Validation with Histopathology

Authors:
Ashraf Anas Zytoon[1][2], Koji Murakami[2], Shingo Hagiwara[3]
(1) Radiology Department, Menoufiya University School of Medicine (Egypt)
(2) PET Center, Dokkyo University School of Medicine (Japan)
(3) Surgical Department, Dokkyo University School of Medicine (Japan)

Correspondence
Ashraf Anas Zytoon
Zip code 321-0293
Kitakobayashi 880
Mibu machi - Shimotsuga gun - Tochigi ken
Japan
Dokkyo University School of Medicine
PET Center
Telephone: 0081-282-85-1168
Fax: : 0081-282-85-1170

ABSTRACT
Purpose: To investigate the detection accuracy of head and neck cancer and lymph node metastasis by FDG-PET compared with CT and MRI, and to validate the results with the histopathological data.
Patients and Methods: Twenty six patients with head and neck cancer were enrolled. Our patients presented for primary staging of head and neck cancer (n=12) or detection of recurrence after radiation/chemotherapy (n=14). Three imaging modalities (FDG-PET, MRI and CT) were compared.
Results: For primary cancer/recurrence detection, the sensitivity for FDG-PET/MRI/CT was the same (100%) while the specificity was 100/100/67%. For lymph node metastasis, the sensitivity for FDG-PET/MRI/CT was 100/67/70% while the specificity was 79/90/67%. FDG-PET also detected distant metastases (liver, paraaortic lymph nodes, and bone metastases) in 3 patients and synchronous tumor (breast cancer) in one patient.
Conclusion: Compared with CT and MRI, FDG-PET was found to have the same sensitivity for primary cancer/recurrence detection, however, it was the most sensitive modality for detection of lymph node metastasis. Moreover, the whole-body FDG-PET imaging proves a useful tool for detection of distant metastasis and synchronous tumors.

Key Words: FDG-PET, lymph node metastasis, head and neck cancer, CT, MRI.

Introduction

Head and neck carcinomas constitute approximately 5% of all malignancies worldwide[1]. Squamous cell carcinoma (SCC) is the major histological type of neoplasm arising from the head and neck area. Lymph node involvement is the most important prognostic factor affecting survival in evaluating patients with head and neck cancer. The average 5-year survival is >50% in patients without, but only 30% in patients with cervical lymph node metastases[2].

CT and MRI are the standard techniques that provide structural information at a high spatial resolution and are therefore used routinely in the initial staging of tumors in these patients. On the other hand, they rely on certain criteria, such as nodal size and contrast-enhancement patterns, that are not very specific[3]. For instance, specificities of as low as 39% for CT and 48% for MRI have been reported for the detection of nodal metastases in patients with head and neck cancer[4].

After radiation/chemotherapy, changes in tumor metabolism precede morphologic changes. Similarly, after radical surgery or radiation therapy for head and neck malignancies, normal tissue planes are altered substantially. Therefore, CT and MRI have relatively poor specificity in the assessment of residual or recurrent disease following radical therapy[5]. Positron emission tomography (PET), on the other hand, helps in evaluation of tumor metabolism. For these reasons, FDG-PET with the glucose analogue fluorodeoxyglucose (FDG) has been used successfully for the assessment of tumor aggressiveness[6], staging of nodal disease in the neck[2,7], treatment evaluation[6], and detection of recurrent disease[8] in patients with head and neck cancer. Unfortunately, the lack of

anatomic detail remains a major limitation of PET if used without CT fusion.

Fluorine-18 fluorodeoxyglucose (18F-FDG) is a marker of tumor viability, based upon the increased glycolysis that is associated with malignancy as compared with most normal tissues. It has also been suggested that tumors with increased FDG uptake appear more aggressive and are associated with less favorable prognosis[2]. Head and neck carcinomas have high glycolytic activity and increased FDG uptake[9]. Therefore, 18FDG-PET has been advocated more and more acceptance as an additional diagnostic tool in the staging of head and neck carcinoma and for the staging of otherwise N0 necks[10]. However, to interpret FDG-PET images accurately, it is essential to be fully familiar with the normal patterns of physiologic tracer uptake, intensities, and frequencies of FDG distribution in the head and neck area[11].
In view of the foregoing, our aim in this study is to compare CT, MRI, and FDG-PET for the detection of head and neck cancer and lymph nodes metastasis and to validate the results with histopathological data.

Patients and Methods

Patients Characteristics And Study Design

The study group included 26 patients (18 male and 8 female). They were referred to Radiology Department, National Cancer Center Hospital East, Japan, for diagnostic imaging. Mean age was 57.9±12.2 years (range 19-77 years). Various head and neck tumors were investigated **(Table 1)**. Clinical examination was performed by a head and neck surgeon. All were scheduled for surgery, radiation/chemotherapy. Twelve patients were evaluated for initial staging of primary head and neck cancer and 14 patients for recurrence after therapy. Patient's evaluation for detection of recurrence or residual tumor after therapy was performed not less than 8 weeks after therapy to avoid post operative or post radiation inflammatory reaction.

Table 1. Data for Individual Patients

No.	Sex	Age	Diagnosis	Pathology	Type
1	F	66	Nasal Ca.	Olfactory Neuroblastoma	Recurrent
2	M	19	Tongue Ca.	SCC	Primary
3	F	52	Hypopharyngeal Ca.	SCC	Primary
4	F	69	Maxillary Sinus Ca.	Malignant Melanoma	Recurrent
5	M	60	Hypopharyngeal Ca.	SCC	Recurrent
6	M	31	Parotid Ca.	Adenoid Cystic Carcinoma	Recurrent
7	F	65	Oropharyngeal (Tonsillar) Ca.	Lymphoma	Primary
8	M	57	Oropharyngeal Ca.	SCC	Recurrent
9	F	71	Tongue Ca.	SCC	Primary
10	M	47	Nasal Ca.	Olfactory Neuroblastoma	Recurrent
11	M	70	Oropharyngeal (Tonsillar) Ca.	Carcinosarcoma	Primary
12	F	62	Nasopharyngeal Ca.	SCC	Primary
13	F	63	Thyroid Ca.	Follicular Carcinoma	Primary
14	F	56	Thyroid Ca.	Papillary Carcinoma	Recurrent
15	M	67	Pharyngeal Ca.	Undifferentiated SCC	Recurrent
16	M	47	Nasopharyngeal Ca.	Lymphoepithelial carcinoma	Recurrent
17	M	60	Nasopharyngeal Ca.	SCC	Recurrent
18	M	55	Laryngeal Ca.	SCC	Primary
19	M	63	Laryngeal Ca.	SCC	Recurrent
20	M	54	Retromolar Ca.	SCC	Primary
21	M	65	Gingival Ca.	SCC	Recurrent
22	M	77	Laryngeal (Subglottic) Ca.	SCC	Recurrent
23	M	60	Pyriform Sinus Ca.	SCC	Primary
24	M	54	Tongue Ca.	SCC	Primary
25	M	62	Hypopharyngeal Ca.	SCC	Primary
26	M	54	Laryngeal (Glottic) Ca.	SCC	Recurrent

M: Male, F: Female, Ca.: Cancer, SCC: Squamous cell carcinoma.

Image Acquisition

Three imaging modalities (CT, MRI and FDG-PET) were used for diagnosis; CT and FDG-PET in 6 patients, MRI and FDG-PET in 9 patients, CT, MRI and FDG-PET in 10 patients, FDG-PET only in 1 patient.

CT

Scans of the cervical region were obtained in 16 patients with a multi-detector CT scanner (Toshiba Acquilion 16 row). Slice thickness was 4–5 mm. Contrast material enhancement was achieved by intravenous administration of 100 ml of non-ionic contrast material Iopamidol 300 (Iopamiron 300; Schering, Osaka, Japan), or Omnipaque 300 (iohexol; Daiichi Pharmaceutical, Tokyo, Japan) with a power injector rate of 2 ml/sec.

MRI

Nineteen patients underwent MRI with a 1.5-T unit (Signa; Philips). We first obtained non-enhanced transversal slices with fast spin-echo technique or gradient echo (T2-weighted slices) with a slice thickness of 5 mm (gap 2 mm). In addition, coronal slices (T1weighted) were performed with a slice thickness of 5 mm and interslice gap 2 mm. All patients had transversal T1-weighted slices before and after intravenous administration of contrast medium [0.1 mmol of gadolinium diethylenetriamine penta-acetic acid (Gd-DTPA)/kg body weight; slice thickness 5 mm and interslice gap 1.4 mm].

FDG-PET

FDG-PET study was performed in all patients (n = 26). They were scanned on GE Advance NXi full-ring PET camera (GE Medical Systems, Waukesha, Wis., USA). PET camera has an axial field-of-view 15.2 cm, transaxial 55 cm and spatial resolution of 5 mm full-width at half-maximum at the centre of the field of view (slice thickness 5 mm). Prior to the 18F-FDG-PET, patients had been fasting for 6 hours. Patients with known diabetes mellitus were excluded from the study, so normal glucose plasma levels (<100 mg%) were confirmed in all patients. The patients were instructed not to chew or talk during the FDG uptake time in order to minimize muscular uptake. Patients were asked to evacuate the urinary bladder before the scan, which was acquired from the pelvic floor to the head. Forty-five up to sixty minutes after intravenous administration of 230-300 MBq 18F-FDG, PET studies were performed using a whole-body technique (six to seven bed positions; acquisition time per position: 4 min; 3 min for emission, 1 min for transmission). In addition, static regional scans of the head and neck region with attenuation correction were acquired by means of a transmission scan acquired by the built-in germanium-68 sources. Attenuation data were segmented (conventional transmission scan) and all images were reconstructed using an iterative algorithm (OSEM, 28 subsets, two iterative steps). FDG was produced in-house using a 18-MeV Cyclotron and an automated FDG synthesis module (HM-18 Cyclotron, Sumitomo Heavy Industries, Japan). The original transverse images were three-dimensionally reconstructed by filtered back-projection.

Image Interpretation and Analysis

CT, MRI and FDG-PET imaging were interpreted individually without knowledge of the other techniques findings. Results of conventional imaging were classified preoperatively according to the TNM classification. Malignancy of primary tumors and lymph nodes were diagnosed using established morphologic criteria including a lymph node size larger than 10 mm, a conglomeration of a minimum of three lymph nodes, central necrosis, indistinct nodal margins[4,9] or if pathological contrast material enhancement was encountered. For lymph node staging, we used the standard VII levels AJCC classification (American Joint Committee on Cancer).

Histopathological examination

All resected tissues (open or excision biopsy) were exactly localized and documented to allow correlation between histopathological results and imaging findings. Classification of the primary tumor and regional lymph node metastases was based on the TNM system of the International Union Against Cancer. Histopathologic results were taken as the gold standard of diagnostic accuracy for CT, MRI and FDG-PET.

Results

Primary Tumor and Local recurrence Detection

MRI and FDG-PET correctly detected primary tumor and local recurrence with high sensitivity and specificity of 100%, CT failed to differentiate between post operative granulation tissue from local recurrence in one patient (100% sensitivity, 67% specificity). Although the negative predictive value was higher for FDG-PET and MRI than CT (FDG-PET = 100%, MRI = 100%, CT = 93%), all three modalities had equally high positive predictive value (FDG-PET, CT and MRI = 100%) **(Table 2)**.

(Fig. 1) 77-years-old man with subglottic carcinoma, status post laryngectomy. Transaxial scans. a. Contrast enhanced CT. b. FDG-PET. Local tumor recurrence was detected by CT and PET (arrows). Lymph node metastasis only picked up by FDG-PET (arrow head).

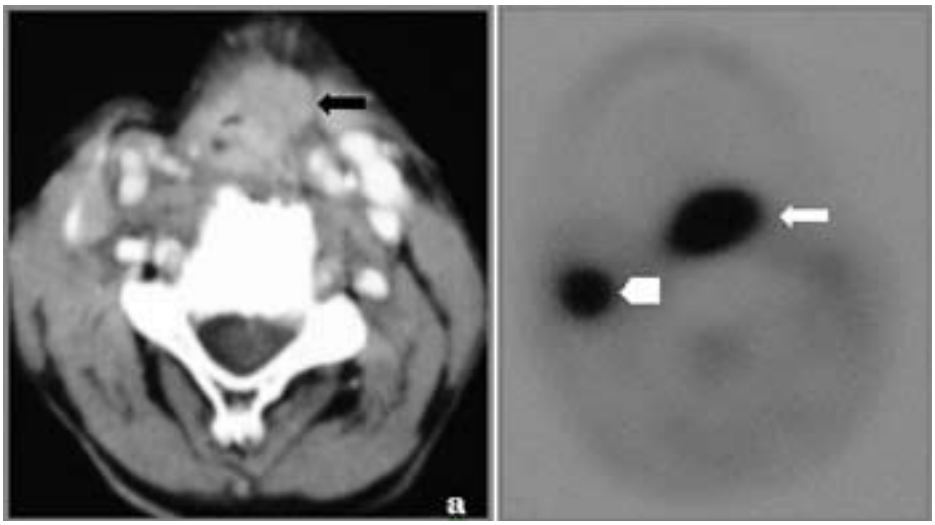


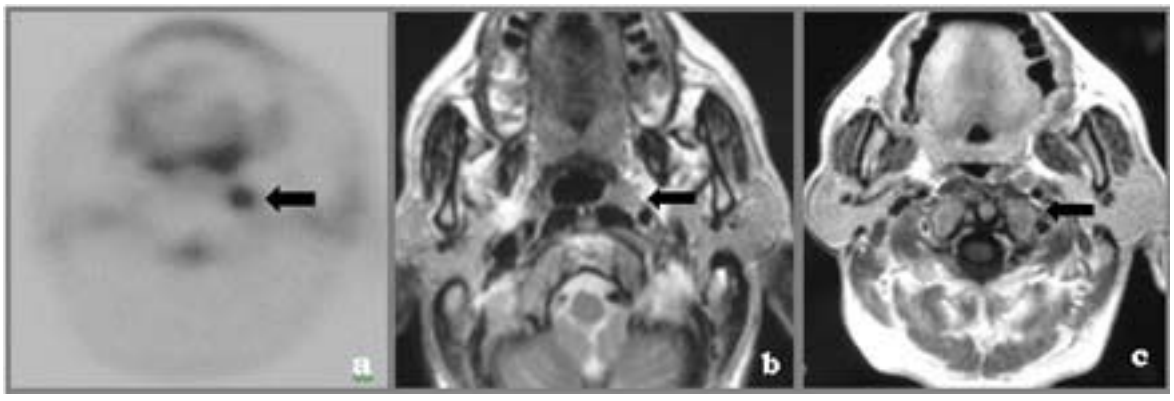
Figure 1

Lymph Node Staging

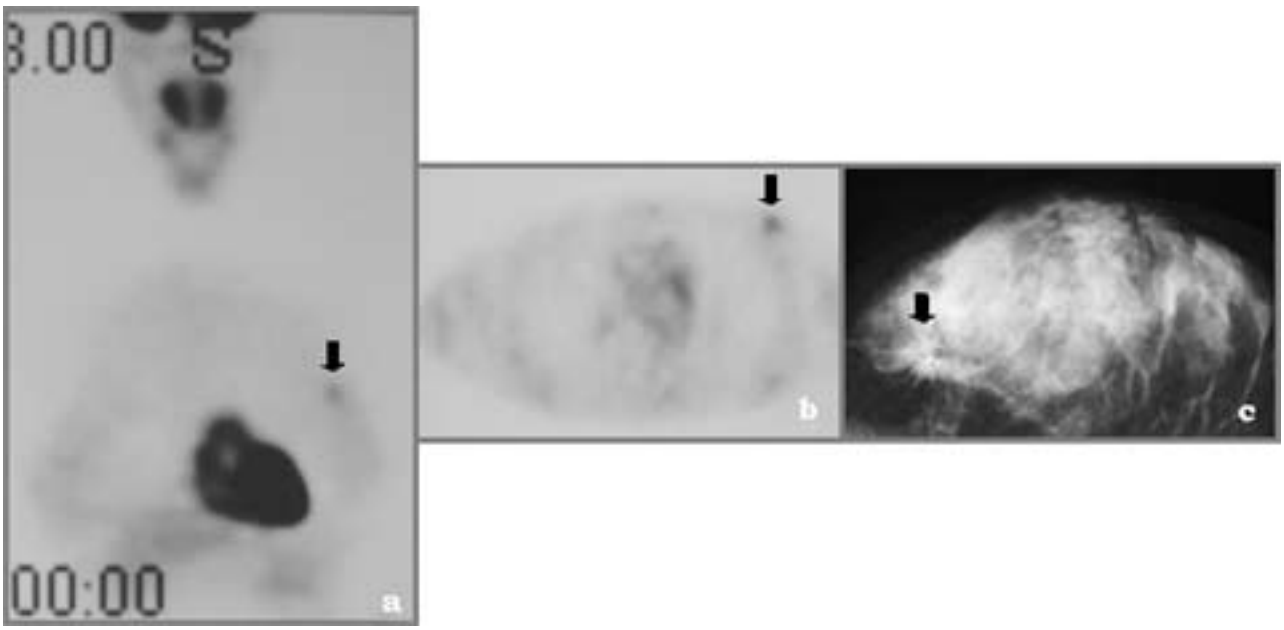
According to the histopathological examinations, there are lymph node metastasis in 12 patients while the rest of patients (n=14) are N0. According to imaging, the sensitivity of CT (7/10; 70%) was almost identical to that of MRI (6/9; 67%). FDG-PET scored the highest sensitivity (12/12; 100%). For the specificity; MRI was the most specific (90%; 9/10) than FDG-PET (79%; 11/14) and CT (67%; 4/6). In 3 locations FDG-PET showed focal lymph node uptake and these findings were assigned as false-positive, which caused by non cancerous inflammatory reaction (pathologically confirmed). From these 3 false-positive cases, 2 were correctly diagnosed by MRI. Although the positive predictive value was higher for MRI (MRI = 86%, FDG-PET = 80%, CT = 78%), the highest negative predictive value was achieved by FDG-PET (FDG-PET = 100%, MRI = 75%, CT = 57%) **(Table 2)**. All false-negative (underestimated) metastatic lymph nodes by CT (n=3) or MRI (n=1), were correctly evaluated by FDG-PET. FDG-PET was more efficient for nodal factor assessment than MRI or CT. FDG-PET.

Distant Metastasis and Synchronous Malignancy Detection

Only FDG-PET by its unique advantage as a whole-body examination detected distant metastases (liver, para-aortic lymph nodes, and bone metastases) in 3 patients, and synchronous breast cancer in one patient.
image... Post operative granulation tissue could not be differentiated form lymph node metastasis, c. MRI T1W axial image 18 months post operative... Left Revenuer's lymph node metastasis becomes clear.



(Fig. 2) 67-year-old man with history of oropharyngeal carcinoma which was treated surgically. PET was ordered for evaluation of potentially recurrent or metastatic disease. a. PET axial scan 8 months post-operative... Abnormal left parapharyngeal hot spot (early detection of left Revenuer's lymph node metastasis), b. Concurrent MRI T2W axial



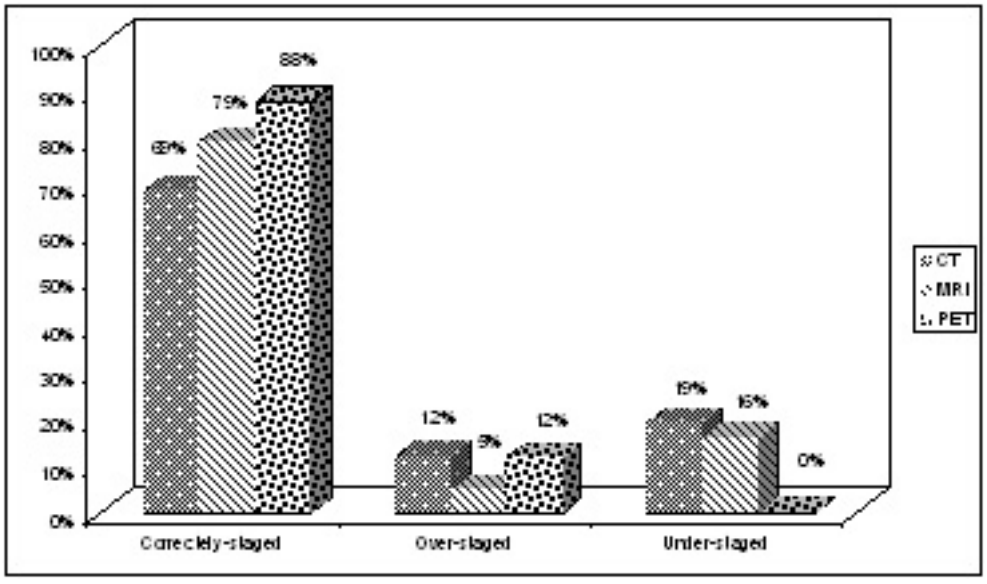
(Fig.3) 65-year-old women with thyroid papillary carcinoma. PET scanning (a. coronal image, b. axial image) easily depicts synchronous second tumor at the left breast. c. Mammography (craniocaudal projection) later shows microcalcifications of malignant pattern at the tumor site. Invasive ductal carcinoma was confirmed after mastectomy.

Table 2. Diagnostic accuracy of primary tumors/recurrence and lymph node metastasis by CT, MRI and FDG-PET

	Primary Tumor/Local Recurrence				Cervical Lymph Node Metastasis			
	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
CT (n=16)	100%	67%	93%	100%	70%	67%	78%	57%
MRI (n=19)	100%	100%	100%	100%	67%	90%	86%	75%
FDG-PET (n=26)	100%	100%	100%	100%	100%	79%	80%	100%

PPV : Positive Predictive Value NPV : Negative Predictive Value

In comparative analysis of accuracy for local lymph node metastasis assessment, nodal factor was correctly estimated by CT in 11/16 patients (true positive n=7, true negative n=4), by MRI in 15/19 patients (true positive n=6, true negative n=9) and by FDG-PET in 23/26 patients (true positive n=12, true negative n=11). Nodal factor over-staging was not frequent (CT 2/16, MRI 1/19 and FDG-PET 3/26). Nodal factor under-staging was slightly higher among CT (3/16) and MRI (3/19) but not FDG-PET (0/26). Imaging outcome was confirmed by histopathological findings **(Fig. 4)**.



(Fig. 4) Assessment of cervical lymph node metastasis by CT, MRI and FDG-PET

Discussion

The present management of head and neck cancer mainly consists of resection of the primary tumor, which may be coupled with neck surgery or subsequent radiotherapy and chemotherapy. When distant metastasis is detected preoperatively, appropriate palliation instead of surgical excision or neck dissection is indicated. Therefore, a decision regarding curative or palliative treatment is crucial for untreated head and neck cancer patients.

Primary head and neck tumors could be detected easily by clinical examination. Additional information about tumor extension into the deep spaces, the relationship to adjacent structures, and bone infiltration is needed for treatment planning. Both MRI and CT met these requirements in all tumors of our series. FDG-PET had no additional value in this situation because of the lack of morphologic information[12]. CT or MRI, by virtue of their higher anatomic resolution, remain the methods of choice for evaluation of the primary tumor with reliable T-staging in 80%–90% of cases[13].

Superior diagnostic accuracy of FDG-PET for primary staging of head and neck cancer patients, metastatic lymph nodes and tumor recurrence has been shown by many authors[8, 14-18]. However, only a few studies have reported the sensitivity of FDG-PET for preoperative staging of primary head and neck cancer and/or compared it with the conventional diagnostic modalities, for example, functional images such as 67Ga and bone scintigraphy, as well as anatomic images such as CT and MRI[19, 20, 21, 22, 23]. These clinical series have been too small to allow statistical comparison or did not apply high-end CT or MRI techniques[12]. The prognosis for patients with head and neck cancer is strongly influenced by the presence of lymph node metastases[19], therefore, we focused the aim of our study on metastatic lymph node work up.

Tumor Staging

It is evident from the literatures[21, 24, 7, 25] that FDG-PET is very sensitive for detecting primary tumors in head and neck region, and our data further supports these findings. Our data demonstrates an accuracy, 100% for FDG-PET in the detection of clinically diagnosed primary tumors, 100% for MRI and 94% for CT in this setting. Our results demonstrate that CT, MRI and FDG-PET can detect all primary tumors or local recurrence with high sensitivity (100%). However, in the detection of metastatic cervical lymph nodes, 30% of the metastatic nodes were missed using CT (70% sensitivity), 33% by using MRI (67% sensitivity). On the contrary no metastatic lymph node missed by FDG-PET (100% sensitivity).

In our series, the sensitivity and specificity of FDG-PET diagnoses were significantly higher than those of CT. Previous reports[7, 19-22, 26-27] showed that FDG-PET had a higher sensitivity (range, 78%–100%) than did CT and MRI (57%–82%). Also, Yoshimasa et al. 2003, in his study compared the FDG-PET sensitivity with CT and MRI for detection of head and neck carcinoma, concluded that the sensitivity of FDG-PET for primary tumor detection was 100% (similar to our results) and it was lower for MRI and CT, 78.3% and 68.2% respectively (lower than our results)[23]. The higher CT and MRI sensitivity recorded in our series, could be explained in view of technical improvement (CT examinations was performed by using 16 mutislice CT scanner with high spatial resolution, moreover, the MR examinations were performed by using 1.5-T machine, which ensure higher image quality (higher signal-to-noise ratio, better spatial resolution through lowering the section thickness and increasing image matrices). Cumulative experience is another important factor due to pooling of many cancer patients to our hospital (National Cancer Center, Japan). MRI and FDG-PET provided similar specificity, levels of confidence, and potential for primary tumor detection.

Precise evaluation of the presence or absence of residual viable tumor is particularly important to the preservation of vital organs and functions by avoiding unnecessary surgery or performing a reduced form of surgery after neoadjuvant chemoradiotherapy. Fourteen out of the total patients were investigated for detection of residual tumors or local recurrence after therapy (monitoring). FDG-PET, MRI and CT had almost equal sensitivity (100%). However, in patients with no viable tumor cells, the specificity of posttreatment FDG-PET (100%) was similar to MRI (100%) but superior to CT (67%), since by CT alone we can not differentiate post operative reaction from residual tumor in one patient. These sensitivity and specificity rates regarding estimation of tumor recurrence are in agreement with Yoshimasa results, except for MRI specificity as he recorded 41.2% specificity for MRI[23]. This difference is mainly due to a different number of recurrence free patients (true negative) examined by MRI between the two studies (n=5 for our study, n=17 for Yoshimasa study). Another factor is the therapeutic approach; most of our patients are treated surgically and evaluated post-surgically while all of the patients in Yoshimasa series are treated by radiotherapy and chemotherapy.

Yoshimasa et al. 2003 settled the superiority of FDG-PET in the investigation of the floor of the mouth, the parapharyngeal space, the base of the tongue, and the cheek where these areas were sometimes difficult to assess using anatomic imaging because posttreatment fibrosis, diffuse edematous swelling, and granulation tissue demonstrated such contrast enhancement could not differentiate the persistent residual tumor[23]. Also the artifact created by teeth is a problem during CT and MRI examination

that could mask important data. FDG-PET correctly identified residual tumors independent of their site and can exclude residual tumors with high specificity.

We agree with Yoshimasa et al. 2003 in his conclusion, that increased FDG uptake on FDG-PET images obtained >4 wk after treatment strongly indicated the presence of residual tumor, whereas the absence of FDG uptake suggested that no viable tumor remained[23].

Lymph Node Staging

Similar to the results of the previous reports[2, 12], metastatic lymph node disease was confirmed in approximately half of the patients in our series. Complete removal of all metastatic lymph nodes is a prerequisite to achieve curative treatment. Morphologic imaging methods, including CT and MRI, are reported to provide a high rate of false-negative diagnoses, which can be explained by micrometastases within otherwise normal lymph nodes[4, 9]. It should be noted that more than 40% of all lymph node metastases are localized in nodes smaller than 1.0 cm in diameter[28]. According to many authors, the smallest lymph node metastasis detected by CT was only 1 cm in diameter, whereas FDG-PET, as functional imaging, was able to localize smaller lymph node metastases (4-6 mm in diameter)[2, 9, 29, 30]. On the other hand, false-negative FDG-PET results were reported in large lymph nodes up to 20 mm in diameter[29] or in necrotic lymph nodes[9]. The reported sensitivities of FDG-PET for nodal disease range from 67% to 91%[2, 9, 21-22, 26, 29-31], similar values were found for CT (67-90%)[2, 4, 9, 29, 32] and MRI (71-91%)[2, 4, 9, 19, 26]. The results of our series are within this range with slightly higher sensitivity for FDG-PET.

The reported specificity of FDG-PET ranges from 88% to 100%[2, 21, 26, 29, 30] (79% for the current study) compared with a wide range of reported specificity values for CT (38-97%) (67% for the current study) and MRI (48-94%) (90% for the current study)[2, 4, 29, 33]. Slightly lower specificity for FDG-PET in the current study might be explained in view of the inhomogeneity of the examination protocols or the difference in the number of patients included in each series.

In accordance with the most published articles[2, 9, 21-22, 24, 26, 29, 34-36], in our study, FDG-PET was significantly superior to CT/MRI for identifying metastatic neck lymph nodes (100% sensitivity for FDG-PET versus 67% for MRI and 70 % for CT). However, Shu-Hang et al. 2005, report lower sensitivity for FDG-PET just 74.7% (but still higher than CT/MRI 52.6%)[25]. Shu-Hang study focused his study on oral cavity SCC and the mean nodal size in his study was relatively small to be detected by FDG-PET.

Previous studies (37-38) showed that the extent of the intranodal tumor deposit is a more limiting determinate to surgical dissection than the nodal size. FDG-PET has been reported to have a higher specificity than CT/MRI in detecting cervical nodal disease in most of the published literature[2, 7, 9, 21-22, 24, 26, 29, 34-35, 37]. Three articles[25, 30, 36] reported that, FDG-PET had a lower specificity. Our study showed the specificity of FDG-PET was lower than MRI (79% vs. 90%) but higher than CT (79% vs. 67%). False-positive FDG-PET findings were mainly due to its inherent inability to discriminate inflammatory processes from tumor infiltration since high-level metabolic changes occur in both instances. Spatial inaccuracy contributed to a portion of the false-positive results.

Table 3. Sensitivity and specificity of CT, MRI, and FDG-PET for diagnosis of head and neck lymph node metastasis, Current literatures report

Author	Patients Total (n)	CT		MRI		FDG-PET	
		sensitivity	specificity	sensitivity	specificity	sensitivity	specificity
Laubenbacher et al. 1995[26]	22	-	-	78%	71%	90%	96%
Braams et al. 1995[30]	12	-	-	36%	94%	91%	88%
Wong et al. 1997[21]	54	67%	25%	67%	25%	67%	100%
Adams et al. 1998[2]	60	82%	85%	80%	79%	90 %	94%
Yoshimasa et al., 2003[23]	23	-	76.2 %	-	85 %	-	73.9 %
Shu-Hang et al., 2005[25]	124	52.6 %	93 %	52.6 %	93 %	74.7 %	94.5 %
Current study	26	70 %	67 %	67 %	90 %	100 %	79 %

Distant Metastatic Workup and Secondary tumors

As for whole-body evaluation, FDG-PET has a clinical impact on the management of patients with head and neck cancer through reliable detection of second primary malignancies as well as distant metastases[39]. FDG-PET with whole-body imaging would replace the conventional functional imaging modalities of 67Ga and bone scintigraphy.

Synchronous secondary tumors are found in about 8% of all head and neck malignant carcinomas[40, 41]. In his series, Florian 2005[12], a simultaneous malignancy was histologically confirmed in five (8.5%) of the 59 patients, including three lesions outside the head and neck region. Regarding our study, there is only one patient (4%) with synchronous tumor (breast cancer) and 3 patients (11.5%) with distant metastases (liver, para-aortic lymph nodes, bone metastases). All were outside the head and neck region. Similar to Florian 2005[12] in his series, all of the synchronic tumors and the distant metastasis were clearly diagnosed by a FDG-PET whole-body scan and missed by the initial CT and MRI examinations of the head and neck region.

Conclusion

This histopathologically controlled study proves FDG-PET as the procedure with the highest sensitivity for detecting lymph node metastases of head and neck cancer and has become a routine method in our National Cancer Center. Although FDG-PET provides information not available by means of MRI or CT, it cannot replace these anatomic modalities. We conclude that FDG-PET and MRI or CT are essential imaging tools for the management of head and neck cancer. In view of our experience, we think that FDG-PET is a highly sensitive exam and if combined with CT as the new era of PET-CT combinations scanners, its accuracy for cancer staging definitely will be increased.

References

1. Peter EV, Dale LB, David WT, et al. Positron Emission Tomography. Basic Science and Clinical Practice. 2004;27: 535-546
2. Adams S, Baum RP, Stuckensen T, Bitter K, Hör G. Prospective comparison of 18F-FDG-PET with conventional imaging modalities (CT, MRI, US) in lymph node staging of head and neck cancer. Eur J Nucl Med 1998;25:1255 -1260
3. Heiko Scho¨der, MD, Henry W. D. Yeung, MD, Mithat Gonen, PhD, Dennis Kraus, MD, Steven M. Larson, MD: Head and Neck Cancer: Clinical Usefulness and Accuracy of PET/CT Image Fusion. Radiology 2004; 231:65–72.
4. Curtin HD, Ishwaran H, Mancuso AA, Dalley RW, Caudry DJ, McNeil BJ. Comparison of CT and MRI in staging of neck metastases. Radiology1998; 207:123 -130
5. Ojiri H, Mendenhall WM, Mancuso AA. CT findings at the primary site of oropharyngeal squamous cell carcinoma within 6–8 weeks after definitive radiotherapy as predictors of primary site control. Int J Radiat Oncol Biol Phys 2002; 52:748–754.
6. Brun E, Kjellen E, Tennvall J, et al. FDG-PET studies during treatment: prediction of therapy outcome in head and neck squamous cell carcinoma. Head Neck 2002; 24:127–135.
7. Hannah A, Scott AM, Tochon-Danguy H, et al. Evaluation of 18 F-fluorodeoxyglucose positron emission tomography and computed tomography with histopathologic correlation in the initial staging of head and neck cancer. Ann Surg 2002; 236:208–217.
8. Wong RJ, Lin DT, Schoder H, et al. Diagnostic and prognostic value of 18F-fluorodeoxyglucose positron emission tomography for recurrent head and neck squamous cell carcinoma. J Clin Oncol 2002;20:4199 -4208
9. Jabour BA, Choi Y, Hoh CK, et al. Extracranial head and neck: PET imaging with 2-[F-18]fluoro-2-deoxy-D-glucose and MRI correlation. Radiology 1993; 186: 27–35.
10. Myers LL, Wax MK, Nabi H, Simpson GT, Lamonica D. Positron emission tomography in the evaluation of the N0 neck. Laryngoscope 1998;108:232-236.
11. Yuji Nakamoto, MD, PhD Mitsuaki Tatsumi, MD, PhD Dima Hammoud, MD Christian Cohade, MD Medhat M. Osman, MD, PhD Richard L. Wahl, MD. Normal FDG Distribution Patterns in the Head and Neck: PET/CT Evaluation. Radiology 2005; 234:879-885
12. Florian Dammann, Marius Horger, Marcus Mueller-Berg, et al. Rational Diagnosis of Squamous Cell Carcinoma of the Head and Neck Region: Comparative Evaluation of CT, MRI, and 18FDG-PET. AJR 2005;184:1326–1331
13. Steinkamp HJ, Maurer J, Heim T, et al. Magnetic resonance tomography and computerized tomography in tumor staging of mouth and oropharyngeal cancer. HNO. 1993;41:519–525.
14. Anzai Y, Minoshima S, Wolf GT, Wahl RL. Head and neck cancer: detection of recurrence with three-dimensional principal components analysis at dynamic FDG-PET. Radiology1999; 212:285 -290
15. Lapela M, Eigtved A, Jyrkkio S, et al. Experience in qualitative and quantitative FDG-PET in follow-up of patients with suspected recurrence from head and neck cancer. Eur J Cancer2000; 36:858 -867
16. Schwartx DL, Rajendran J, Yueh B, et al. Staging of head and neck squamous cell cancer with extended-field FDG-PET. Arch Otolaryngol Head Neck Surg. 2003;129:1173–1178
17. Kresnik E, Mikosch P, Gallowitsch HJ, et al. Evaluation of head and neck cancer with 18F-FDG-PET: a comparison with conventional methods. Eur J Nucl Med. 2001;28:816–821
18. Bar-Shalom R, Valdivia AY, Blaufox MD. PET imaging in oncology. Semin Nucl Med. 2000;30:150–185
19. Rege S, Maass A, Chaiken L, et al. Use of positron emission tomography with fluorodeoxyglucose in patients with extracranial head and neck cancers. Cancer 1994; 73:3047-3058
20. Paulus P, Sambon A, Vivegnis D, et al. 18FDG-PET for the assessment of primary head and neck tumors: clinical, computed tomography, and histopathological correlation in 38 patients. Laryngoscope1998; 108:1578 -1583
21. Wong WL, Chevretton EB, McGurk M, et al. A prospective study of PET-FDG imaging for the assessment of head and neck squamous cell carcinoma. Clin Otolaryngol. 1997; 22:209 -214
22. Bailet JW, Abemayor E, Jabour BA, Hawkins RA, Ho C, Ward

PH. Positron emission tomography: a new, precise imaging technique for detection of primary head and neck tumors and assessment of cervical adenopathy. Laryngoscope 1992; 102:281 -288

23. Yoshimasa Kitagawa, Sadahiko Nishizawa, Kazuo Sano, et al. Prospective Comparison of 18F-FDG-PET with Conventional Imaging Modalities (MRI, CT, and 67Ga Scintigraphy) in Assessment of Combined Intraarterial Chemotherapy and Radiotherapy for Head and Neck Carcinoma. Journal of Nuclear Medicine 2003 Vol. 44 No. 2 198-206
24. Nowak B, Martino ED, Janicke S, et al. Diagnostic evaluation of malignant head and neck cancer by F-18-FDG-PET compared with CT/MRI. Nuklearmedizin. 1999;38:312–318
25. Shu-Hang Ng, Tzu-Chen Yen, Chun-Ta Liao, et al. 18F-FDG-PET and CT/MRI in Oral Cavity Squamous Cell Carcinoma: A Prospective Study of 124 Patients with Histologic Correlation. Journal of Nuclear Medicine 2005; Vol. 46 No. 7 1136-1143
26. Laubenbacher C, Saumweber D, Wagner MC, et al. Comparison of fluorine-18-fluorodeoxyglucose PET, MRI and endoscopy for staging head and neck squamous-cell carcinomas. J Nucl Med. 1995; 36:1747–1757
27. Keyes JW Jr, Watson NE Jr, Williams DW 3rd, Greven KM, McGuirt WF. FDG-PET in head and neck cancer. AJR. 1997;169:1663–1669.
28. Van den Brekel MW, Castelijns JA, Snow GB. Imaging of cervical lymphadenopathy. Neuroimaging Clin North Am 1996; 6: 417–434.
29. Benchaou M, Lehmann W, Slosman DO, Becker M, Lemoine R, Rufenacht D, Donath A. The role of FDG-PET in the preoperative assessment of N-staging in head and neck cancer. Acta Otolaryngol 1996; 116:332-335
30. Braams JW, Pruim J, Freling NJ, et al. Detection of lymph node metastases of squamous-cell cancer of the head and neck with FDG-PET and MRI. J Nucl Med 1995; 36:211 -216
31. Pöpperl G, Lang S, Dagdelen O, et al. Correlation of FDG-PET and MRI/CT with histopathology in primary diagnosis, lymph node staging and diagnosis of recurrency of head and neck cancer [in German]. Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 2002; 174:714 -720
32. McGuirt WF, Williams DW 3rd, Keyes JW Jr, et al. A comparative diagnostic study of head and neck nodal metastases using positron emission tomography. Laryngoscope1995; 105:373 -375
33. Van den Brekel MW. Lymph node metastases: CT and MRI. Eur J Radiol 2000; 33:230 -238
34. Kau RJ, Alexiou C, Laubenbacher C, Werner M, Schwaiger M, Arnold W. Lymph node detection of head and neck squamous cell carcinomas by positron emission tomography with fluorodeoxyglucose F18 in a routine clinical setting. Arch Otolaryngol Head Neck Surg. 1999;125:1322–1328
35. Stokkel MPM, ten Broek FW, Hordijk GJ, et al. Preoperative evaluation of patients with primary head and neck cancer using dual-head 18 fluorodeoxyglucose positron emission tomography. Ann Surg. 2000;231:229–234
36. Hlawitschka M, Neise E, Bredow J, et al. FDG-PET in the pretherapeutic evaluation of primary squamous cell carcinoma of the oral cavity and the involvement of cervical lymph nodes. Mol Imaging Biol. 2002;4:91–98
37. Stuckensen T, Kovacs AF, Adams S, Baum RP. Staging of the neck in patients with oral cavity squamous cell carcinomas: a prospective comparison of PET, ultrasound, CT and MRI. J Craniomaxillofac Surg. 2000;28:319–324
38. Crippa F, Leutner M, Belli F, et al. Which kinds of lymph node metastases can FDG-PET detect? a clinical study in melanoma. J Nucl Med. 2004;41:1491–1494.
39. Kitagawa Y, Nishizawa S, Sano K, et al. Whole-body 18F-fluorodeoxyglucose positron emission tomography in patients with head and neck cancer. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;93:202–207
40. AAssar OS, Fischbein NJ, Caputo GR, et al. Metastatic head and neck cancer: role and usefulness of FDG-PET in locating occult primary tumors. Radiology1999; 210:177 -181
41. Schwartz LH, Ozsahin M, Zhang GN, et al. Synchronous and metachronous head and neck carcinomas. Cancer1994; 74:1933 -1938

Review Articles

Drugs and Older People

Authors:
Peter Crome, Frank Lally

Correspondence:
Keele University Medical School
Courtyard Annexe
City General Hospital
Newcastle Road
Stoke-on-Trent
Staffordshire ST4 6QG
UK
Tel: 01782 553968
Fax: 01782 553978
E-mail: p.crome@keele.ac.uk

Co-author: Dr F Lally PhD
Keele University Medical School
Courtyard Annexe
City General Hospital
Newcastle Road
Stoke-on-Trent
Staffordshire ST4 6QG
UK
Tel: 01782 552499
Fax: 01782 553978
E-mail: f.lally@pmed.keele.ac.uk

ABSTRACT

People are living longer and the proportion of older people in almost all countries is set to rise. As people age they develop diseases and this leads to more prescribing - both to prevent disease progression and for symptomatic relief. However, drug treatment in later life is problematic. There is a dearth of evidence on the efficacy of drugs in the over eighties and this age group is at the highest risk of adverse drug reactions. Many drugs show altered pharmacokinetics and pharmacodynamics. The term "appropriate prescribing" has been introduced to describe a strategy which tries to ensure that all older people receive only medications which are beneficial, whilst at the same time potentially harmful drugs are avoided. Where evidence of benefit does not exist, then a more detailed face to face explanation with the patient is required to ensure that the patient understands the magnitude of the expected benefit and the risks. Priorities may have to be established, particularly if taking the drugs is problematic or because of financial difficulties. Doses will need adjustment in the light of any known pharmacokinetic and pharmacodynamic changes that occur in later life. Attempts have been made to establish lists of drugs that should be avoided in older people because of their extra risks and attempts are being made to ensure that pharmaceutical companies trial their new drugs in older people.

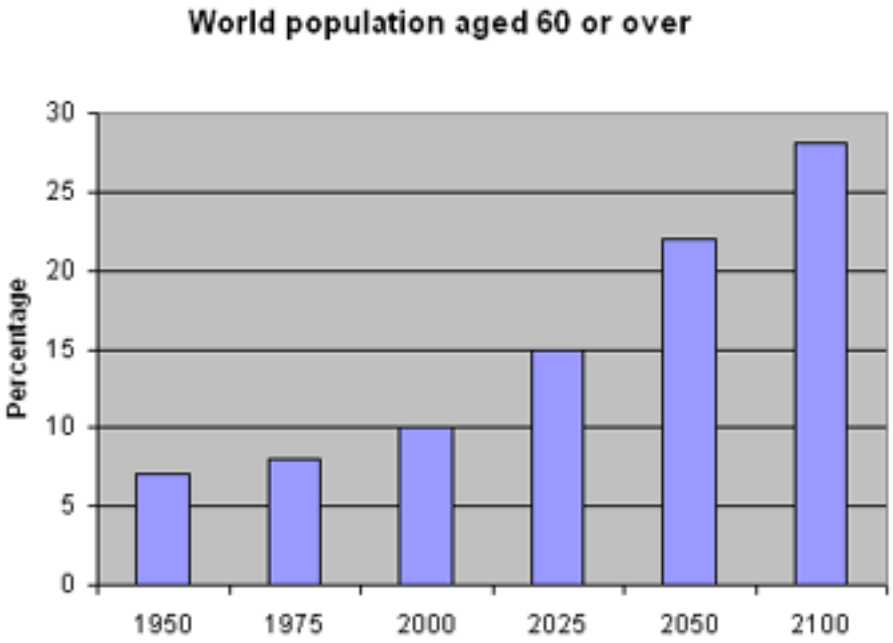
Key words: Drugs, older people, medication, pharmacotherapy, pharmacodynamics.

Introduction

Prescribing for older people poses clinicians with challenges that are not apparent in younger people. Older people are, of course, a heterogeneous group, but they have an increased likelihood of developing illnesses as they age. Illnesses lead to the prescription of drugs, both to treat the symptoms and to prevent further complications. Thus it is not uncommon to find people in their eighties taking ten or more different drugs. Age itself results in physiological changes which affect the way in which the body handles, or reacts to the drugs. These features together with a dearth of robust evidence for the effectiveness of drugs in later life combine to make prescribing more problematic and adverse drug reactions more likely. Strategies to improve prescribing have been developed based on the concept of "appropriate prescribing" in which both under-prescribing and over-prescribing are avoided and the risks of adverse drug reactions are minimised. These issues are discussed in this review.

Demographic predictions **(Figure 1)** indicate that the proportion of the population over 65 will continue to increase both in the UK and elsewhere with the most rapid changes occurring in the developing world[1].

Figure 1: World population ageing
Based on figures provided on the website of The Population Division, Department of Economic and Social Affairs, United Nations Secretariat 2006



The Middle East and North Africa has recorded the highest population growth worldwide over the past century[2]. The proportion of the population over the age of 65 in that region was 4.4% in 2000 and is expected to rise to 8.4% in 2030[3]. One study[4] , looking at changes in use by the elderly (>65) of the ER of a major hospital in Al-Ain in the years 1989 and 1999 found that patient numbers rose from 321 in 1989 to 1347 in 1999. Attendance rose 5.4 fold while non-urgent attendance rose 14.7 fold, demonstrating rising use, but falling illness severity over time.

However, not all people living longer are necessarily living in good health. The difference between life expectancy and healthy life expectancy can be regarded as an estimate of the number of years a person can expect to live in poor health. In 1981 the expected time lived in poor health for a man was 6.5 years. By 2001 this had risen to 8.7 years[5:6]. The good news was that total life expectancy had risen by about five years for men and three years for women over the same time period. Recent figures show that 45% of drugs in the UK are prescribed for people over 65 who themselves make up about 18% of the population[7]. Demographic changes, the development of new classes of medications and Government policies (National Service Frameworks, NICE Guidelines etc) all indicate that prescribing for older people will increase.

Age-Related Physiological Changes: Pharmacokinetics and Pharmacodynamics

Body composition changes with advancing age with the percentage of muscle and body water declining by as much as 25% by the age of 70. Body fat increases. This and other physiological changes influence the pharmacokinetics of drugs in older people **(Table 1)**.

Table 1. Age-related physiological changes

Splanchnic blood flow falls	Liver blood flow falls
Glomerular filtration falls	Liver size falls
Renal blood flow falls	Gastric acidity falls
Renal tubular function falls	Gastric emptying delayed

As a generality the absorption of drugs through the gut is little changed. Distribution is altered with lipid soluble drugs being distributed more widely and being cleared more slowly (e.g. diazepam). On the other hand hydrophilic drugs have reduced distribution volumes and have higher concentrations in body water compartments. Ageing is associated with reduced first-pass metabolism and systemic clearance of many hepatically metabolised drugs can be affected. This is due to a reduction in liver mass and blood flow and results in an increased bioavailability of drugs that undergo first-pass metabolism[8-11]. Conversely, pro-drugs such as ACE-inhibitors, which require activation in the liver, may have lowered systemic concentrations, as more of the inactive parent compound will reach the circulation. The specific content of cytochrome P450 (CYP) enzymes also diminishes during ageing[12]. This combined with reduced blood flows and decreased liver mass may combine to decreased hepatic clearance of drugs in older people.

In addition, many drugs have different racemic forms with the stereo-isomers having different pharmacological properties. Age may have a selective effect on the pharmacokinetics of these different isomers. Age-related changes in the kidney result in altered renal function with age[13;14]. This results in reduced clearance and increased half-life of drugs eliminated predominately by the kidney. Such drugs include digoxin, aminoglycosides and lithium. The pharmacokinetics of new drugs are usually investigated as part of that drug's development but this may not be the case for older medications which sometimes remain the most effective.

The pharmacodynamic effects (what the drug does to the body) of ageing have been less well evaluated than the pharmacokinetic changes. Among the drugs producing a greater effect, are benzodiazepines, anaesthetics and warfarin. On the other hand older people may appear more resistant to the effect of others e.g. beta-receptor agonists and antagonists. These changes may be due to factors at the target organ, or at the receptor level. The overall effects of a drug may also be influenced by changes in body homeostatic mechanisms.

Frailty and Drugs

The earliest studies of pharmacokinetics in old age usually compared young volunteers with hospitalised patients or those in care homes. The marked differences in pharmacokinetics found in these studies result from multiple co-morbidity and frailty and need to be differentiated from those due to age alone, which have a less marked effect. Recently more attention has been paid to the interaction between age and disease and the consequent changes in drug handling as well as the effects of frailty. The latter group are recognised as those older people who have the least functional reserve and are at greatest risk of becoming dependent and moving to institutional care[15]. A decline in metabolic activity of plasma aspirin esterase, the conjugation of paracetamol (acetaminophen) and metoclopramide has been reported in the frail[16-19].

Age Discrimination?

There is ample evidence that older people are not prescribed potentially beneficial drugs such as statins and antihypertensives[20-22]. Additionally the evidence for their efficacy in the very old is lacking[23] so that it is difficult to be dogmatic that these older people are missing out. It is drug regulatory authority guidance that the efficacy of drugs should be evaluated in age groups for which a drug is likely to be prescribed. However, very few drugs have been adequately tested in the over-eighties. This creates a major dilemma for prescribers, particularly if the drug is intended to prevent further complications rather than give immediate symptomatic relief. On the one hand the drug may prove useless or produce side effects if prescribed whilst if it is not given then worthwhile benefit will be missed. Such prescribing dilemmas are not easy to resolve. Discussion with the patient on the established risks and benefits, the relative importance of the treatment under review in relation to other conditions the patient may have and the time course before benefit may be observed are all relevant factors to consider with the patient.

Adverse Drug Reactions

Numerous studies have shown the link between increasing age and increasing frequency of adverse drug reactions (ADR)[24;25]. In addition the consequences may be more serious. For example a fall as a result of excess sedation from a tranquillising drug is more likely to result in a fracture and a gastro-intestinal bleed from a non-steroidal anti-inflammatory drug is more likely to result in a fatal outcome. ADR are common. One study found that of 2,643 hospitalised patients. ADR was detected in 191; of these a fifth were classified as preventable[26]. In the United States Lazarou et al found ADR to be ranked between 4-6 of the leading causes of death in hospitalised older patients[27]. The association between patients' age and the risk of an adverse drug reaction was confirmed by Pirmohammed et al[21] who found that the average age for an admission with an ADR was 76 years compared to 66 years for a patient admitted for other reasons. In this study 16.6% of ADRs were due to a drug interaction, an

important point in a patient group treated with multiple drugs.

Improving Prescribing

One of the approaches that have been advocated to reduce ADRs is the categorisation of certain drugs as "inappropriate" for use in older people. Thus Beers et al in the USA[28] have produced lists of drugs that 1) generally should be avoided in older people, 2) drugs that should be prescribed up to defined daily doses and 3) drugs to avoided when specific co-morbidities exist. The decision as to which drugs should be listed has been achieved through a modified Delphi process and the list has been updated[29]. An obvious disadvantage is that regular updating is required and the translation of the recommendations to other countries may be problematic. For example the latest classification from the USA classifies dypridamole as inappropriate whilst in UK the drug is mandated for use following stroke[29]. A slightly different approach to the development of lists of inappropriate drugs has been described by the ACOVE (Assessing Care of Vulnerable Elders) project[30]. This seeks to identify ill older people and use evidence-based indicators of quality of care to assess the care at the health service level.

In the UK a number of prescribing indicators have been developed which are suitable as a basis for audit in hospital or nursing home settings. Batty et al's indicators include the appropriate use of anti-thrombotics, aspirin and benzodiazepines[31;32]. The National Service Framework for Older People (NSFOP)[33] has set out a series of strategies to improve prescribing. These include active management of medication, regular reviews of repeat prescriptions and greater involvement of pharmacists as well as more education and training. However a recently published independent report on the NSFOP[34] criticised the fact that many older people taking more than four medicines are still not receiving a review every six months.

Audit mechanisms, such as conformity with the British National Formulary, are also recommended.

Compliance and Concordance

One study showed that 50% of drugs prescribed for older people with chronic conditions are not taken[35]. Such "non-compliance" may be deliberate or accidental due to confusion, loss of manual dexterity in removing tablets from packaging and bottles or more likely due to misunderstanding about the nature of the medication and the way it should be taken. The term "compliance" is now regarded as pejorative and "concordance" is now preferred. Underlying the concept of concordance is greater patient involvement in partnership with prescribers[36-38]. A model of concordance has been developed with the aim of achieving agreement regarding the choice and outcomes of treatment[39].

Substance use misuse and dependence

In addition to the many complex interactions discussed above, there is growing recognition of the role of the use of alcohol, nicotine and illicit drugs in older people. It is well documented that each of these substances have physical, psychological, psychiatric and social complications and indeed, may be used as a result of psychosocial distress and medical illness[40]. To further compound the issue older people may be using over the counter and prescribed medication non-compliantly. All these drugs and medications may interact e.g. alcohol and benzodiazepines may predispose to falls.

Thus it is important that practitioners are competent to take a substance misuse history so as to delineate the effects of individual substances and plan treatment appropriately. Failure to be aware of these complicated interrelationships will undoubtedly lead to erroneous diagnostic formulations and deprive older people of the benefit of a wide range of pharmacological and psychological treatments for substance misuse and dependence.

Conclusion

Age-related physiological changes, the presence of co-morbidity and concomitant medication together with an inadequate evidence-base conspire to make prescribing in this age group problematic. Minimising risk and maximising benefit requires knowledge of the effects of each drug a patient might be taking and a degree of pragmatism in decision making. The additional benefits of the ninth or tenth drug should be carefully considered. Probably the best approach is for the patient and the prescriber to review regularly the medication that is being taken and jointly agree which are important drugs to take.

References

1. United Nations -Three Centuries of World Population Ageing. 2000. Ref Type: Generic
2. Population trends and challenges in the middle east and north Africa. Accessed 05 February 2007 . 2001. Ref Type: Internet Communication
3. Kinsella K, Phillips D. Global aging: The challenge of success. 60[1]. 2005. Population Reference Bureau. Ref Type: Report
4. Margolis SA, Reed RL. Changing use of the emergency department by the elderly in the United Arab Emirates, 1989 and 1999. Eastern Mediterranean Health Journal 8, 2-3. 1999. Ref Type: Journal (Full)
5. Office for National Statistics. 2006. Ref Type: Report
6. Government Actuary's Department for expectation of life data. 2004. Ref Type: Report

7. Department of Health Statistics of prescriptions dispensed in the Family Health Service Authorities: England 1989-1999. Statistical Bulletin . 2002. Ref Type: Report

8. Anantharaju A, Feller A, Chedid A. Aging Liver. Gerontology 2002; 48(6):343-353.

9. Zeeh J, Platt D. The Aging Liver. Gerontology 2002; 48(3):121-127.

10. Greenblatt DJ, Harmatz JS, Shapiro L, Engelhardt N, Gouthro TA, Shader RI. Sensitivity to triazolam in the elderly. N Engl J Med 1991; 324(24):1691-1698.

11. Castleden CM, George CF. The effect of ageing on the hepatic clearance of propranolol. Br J Clin Pharmacol 1979; 7(1):49-54.

12. Sotaniemi EA, Arranto AJ, Pelkonen O, Pasanen M. Age and cytochrome P450-linked drug metabolism in humans: An analysis of 226 subjects with equal histopathologic conditions. Clinical Pharmacology & Therapeutics 1997; 61(3):331-339.

13. Kaplan C, Pasternack B, Shah H, Gallo G. Age-related incidence of sclerotic glomeruli in human kidneys. Am J Pathol 1975; 80(2):227-234.

14. Muhlberg W, Platt D. Age-dependent changes of the kidneys: pharmacological implications. Gerontology 1999; 45(5):243-253.

15. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the Concepts of Disability, Frailty, and Comorbidity: Implications for Improved Targeting and Care. J Gerontol A Biol Sci Med Sci 2004; 59(3):M255-M263.

16. Groen K, Horan MA, Roberts NA, Gulati RS, Miljkovic B, Jansen EJ et al. The relationship between phenazone (antipyrine) metabolite formation and theophylline metabolism in healthy and frail elderly women. Clin Pharmacokinet 1993; 25(2):136-144.

17. Williams FM, Wynne H, Woodhouse KW, Rawlins MD. Plasma aspirin esterase: the influence of old age and frailty. Age Ageing 1989; 18(1):39-42.

18. Wynne HA, Cope LH, Herd B, Rawlins MD, James OF, Woodhouse KW. The association of age and frailty with paracetamol conjugation in man. Age Ageing 1990; 19(6):419-424.

19. Wynne HA, Yelland C, Cope LH, Boddy A, Woodhouse KW, Bateman DN. The association of age and frailty with the pharmacokinetics and pharmacodynamics of metoclopramide. Age Ageing 1993; 22(5):354-359.

20. Allen Maycock CA, Muhlestein JB, Horne BD, Carlquist JF, Bair TL, Pearson RR et al. Statin therapy is associated with reduced mortality across all age groups of individuals with significant coronary disease, including very elderly patients. J Am Coll Cardiol 2002; 40(10):1777-1785.

21. Berlowitz DR, Ash AS, Hickey EC, Friedman RH, Glickman M, Kader B et al. Inadequate Management of Blood Pressure in a Hypertensive Population. N Engl J Med 1998; 339(27):1957-1963.

22. Ho SF, O'Mahony MS, Steward JA, Burr ML, Buchalter M. Left ventricular systolic dysfunction and atrial fibrillation in older people in the community - a need for screening? Age Ageing 2004; 33(5):488-492.

23. Crome P, Pollock K. Age-discrimination in prescribing: accounting for concordance. Reviews in Clinical Gerontology 14, 1-4. 2005. Ref Type: Generic

24. Routledge PA, O'Mahony MS, Woodhouse KW. Averse drug reactions in elderly patients. British Journal of Clinical Pharmacology 2004; 57(2):121-126.

25. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004; 329(7456):15-19.

26. Onder G, Landi F, Cesari M, Gambassi G, Carbonin P, Bernabei R. Inappropriate medication use among hospitalized older adults in Italy: results from the Italian Group of Pharmacoepidemiology in the Elderly. Eur J Clin Pharmacol 2003; 59(2):157-162.

27. Lazarou J, Pomeranz BH, Corey PN. Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-analysis of Prospective Studies. JAMA 1998; 279(15):1200-1205.

28. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. Arch Intern Med 1997; 157(14):1531-1536.

29. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults: Results of a US Consensus Panel of Experts. Arch Intern Med 2003; 163(22):2716-2724.

30. Knight EL, Avorn J. Quality indicators for appropriate medication use in vulnerable elders. Ann Intern Med 2001; 135(8 Pt 2):703-710.

31. Batty GM, Grant RL, Aggarwal R, Lowe D, Potter JM, Pearson MG et al. National Clinical Sentinel Audit of Evidence-based Prescribing for Older People. Journal of Evaluation in Clinical Practice 2004; 10(2):273-279.

32. Batty GM, Grant RL, Aggarwal R, Lowe D, Potter JM, Pearson MG et al. Using prescribing indicators to measure the quality of prescribing to elderly medical in-patients. Age Ageing 2003; 32(3):292-298.

33. Department of Health. Medicines and older people - Implementing medicines-related aspects of the NSF for older people. 2001. Ref Type: Report

34. Living well in later life - A review of progress against the National Service Framework for Older People. 2006. Audit commission; Healthcare commission; Commission for Social Care Inspection. Ref Type: Report

35. Brian Haynes R, Ann McKibbon K, Kanani R. Systematic review of randomised trials of interventions to assist patients to follow prescriptions for medications. The Lancet 1996; 348(9024):383-386.

36. Department of Health. The expert patient: a new approach to chronic disease management for the 21st century. 2001. DOH, London. Ref Type: Report

37. Department of Health. Involving patients and the public in healthcare. A discussion document. 2001. DOH, London. Ref Type: Report

38. Department of Health. Patient partnership: Building a collaborative strategy. London DOH . 1996. Ref Type: Report

39. Royal Pharmaceutical Society of Great Britain. From compliance to concordance: achieving shared goals in medicine taking. 1997. London, Royal Pharmaceutical Society of Great Britain. Ref Type: Report

40. McGrath A, Crome P. Substance misuse in the older population. Postgraduate Medical Journal 2005;(81):228-231.

Review Articles

The status of Charitable Health Organizations in Some Islamic countries

Author:
Dr. Seyedvahid Hosseini[1], Dr. Leila Malekmakan[2], Dr. Sezaneh Haghpanah[3]
1. Vice Chancellor for clinical Affaires of Shiraz University of Medical Sciences
2. Member of Shiraz Nephro-urology research center in Shiraz University of Medical Sciences
3. Director of health system research of vice chancellor for clinical affairs of Shiraz university of medical sciences

ABSTRACT:

International charitable work fills critical gaps in the global socioeconomic infrastructure . Governmental organizations alone can not solve every social problem, without international charity , more people in the world would die of hunger , disease and live in poverty .In this paper we study the situation of some charities in Islamic countries .

In *Kuwait*, International Islamic charitable organization (IICO) has branches and offices all over the state. Their strategy is to present an Islamic model of integrated modern charitable work . More than sixty countries around the world are benefiting from IICO charitable work (Such as Jordan, Uganda, Nigeria, Niger, Benin , Comoros Islands and Sudan). In *Bangladesh,* NGOs play a significant role in PHC provision in rural and urban areas. Several hundred indigenous NGOs have been active in health and development since the country's independence in 1971. In *Palestine,* in addition to the public health services available , and those provided by charitable and voluntary organizations , the main providers of health care for the population are the Palestinian Red Crescent Society and other NGOs. In *Iran,* currently, there are also a large number of health facilities, ranging from out patient clinics to hospitals and institutions, run by charitable community groups. Finally considering the successful pattern and strength points of the charities in other countries, especially Islamic countries, help us to promote the status of charity service delivery to the community.

Introduction

International charitable work fills critical gaps in the global socioeconomic infrastructure. Governments alone cannot solve every social problem. Businesses alone cannot meet every economic need. Without international charity, more people in the world would die of hunger and disease, fewer children would learn to read and write, and more people would live in poverty. There would be more environmental destruction and fewer scientific advances[(1)].

The use of private health care providers in low and middle income countries (LMIC) is wide spread and its implications are the subject of continuing debate. One view is that private providers are likely to be more efficient than the public sector and hence that government should contract out services to the private sector. An alternative view is that private providers are often not superior in quality or efficiency to the public sector, and that contracts are not straightforward to design and implement. Finally, there is increasing recognition that neither public nor private providers have uniform characteristics, and that this distinction might overlook more important issues, such as the extent to which a provider uses public funds efficiently and serves the goals of public health[(2)]. The range of charitable services provided is extensive-medical care, food, agricultural training, disaster relief, shelter, education, clothing, water, professional exchanges, and support of human rights and civil liberties.

Each charitable organization must safeguard its relationship with the communities it serves in order to deliver effective programs. This relationship is founded on local understanding and acceptance of the independence of the charitable organization. If this foundation is shaken, the organization's ability to be of assistance and the safety of those delivering assistance is at serious risk[(1)]. A lack of standards in healthcare organizations often makes it difficult to consistently define and report charity care. Accurately documenting services provided to patients who are unwilling or unable to pay can be difficult for many organizations[(3)]. Nowadays we see increasing urgent needs in poor societies especially in Moslem countries and communities where poverty, illiteracy, unemployment, disease, famine and other difficult situations are persisting. In this paper we study the situation of some charities in Islamic countries.

Kuwait

IICO (International Islamic Charitable Organization) is an independent non-political organization which offers a wide range of pure humanitarian services, that was established in Kuwait. IICO was founded to meet the increasing urgent needs in poor societies especially in Moslem countries and communities where poverty, illiteracy, unemployment, diseases, famine, and other difficult situations are persisting.

IICO has established several committees to provide aid in various fields. Each of these committees is specialized in a specific field or serving a geographical area or a particular group of people. The first of these was the Committee of Asia. That is one of the IICO's largest committees, serving 825 million Muslims in Asia. The objective of this committee is helping the needy in the Asian continent, since they represent the largest Muslim community in the world (three quarters of the world Muslims). More than sixty countries around the world are benefiting from IICO's charitable work whether Muslim population is a majority or a minority[4].

Bangladesh

NGOs play a significant role in PHC provision in rural Bangladesh, and they provide most of these services in urban areas. Under the Government of Bangladesh's 5-year Health and Population Sector Programme (HPSP) the overall objective was to improve the health of the population. The Bangladesh Population and Health Consortium (BPHC) agency, which delivers maternal and child health (MCH) and family planning services in rural areas, was established by the British Overseas Development Administration (ODA). From 1998-2003, the UK Department for International Development (DFID) funded BPHC to develop government NGO collaboration in the sector and deliver ESP services through partner NGOs in a Public-NGO Partnership (PNP). This was to be an integral part of the sectoral programme, jointly managed by DFID and the Line Director for ESP-Reproductive Health in the Ministry of Health and Family Welfare (MOHFW).

In the PNP phase, BPHC invited NGOs, to bid for funds to deliver ESP services in areas agreed upon with the government health managers. The MOHFW Line Director was informed of the procedures and arrangements for a transparent selection process, which was implemented by BPHC in 2000. This included visits and interviews with NGO managers, separate financial and technical proposals, and assessment and scoring of these by BPHC and external reviewers. The emphasis was on BPHC supporting the NGOs to provide an expanded range of services consistent with the government ESP, developing government-NGO collaboration and demonstrating the impact of NGO service delivery[5].

Palestine

Because of the dispersal of the Palestinian people across different areas and as a result of the lack of a unified political authority, there are no unified health policies and strategies; rather, the various bodies providing services have their own characteristics. The main providers of health care for the Palestinian population are the Palestinian Red Crescent Society and other Palestinian NGOs and UNRWA. UNRWA's policy is to provide essential health services to eligible Palestinian refugees, consistent with the humanitarian policies of the United Nations and the basic principles and concepts of the WHO.

UNRWA's health system is based on three levels. At the primary level, outpatient services are provided through UNRWA's facilities-general and special care clinics, laboratories and dental clinics, which are integrated at health centre level. At the secondary level, referral and support services comprise inpatient care at subsidized hospitals, as well as specialist and rehabilitative care and other basic support services through contractual arrangements or individual patient subsidies. At the tertiary level, UNRWA provides partial individual patient subsidies for emergency life-saving treatment at the specialized health institutions available in the area of operations, provided this does not involve long-term commitment[6].

Islamic Republic of Iran

Although the NGO movement in its modern sense is relatively new to Iran and most of the active NGOs are closely associated with the government, there is a long tradition of voluntary participation in financing, organization and provision of health services as charitable acts. In fact many of the famous hospitals and health centers established early in the century owe their existence to such charitable organizations predating the established of the MOH&ME. Currently too there are a large number of health facilities, ranging from outpatient clinics to hospitals and institutions run by the charitable community groups.Among the NGOs established over the past few years a considerable number are concerned with health problems related to specific groups like Thalassaemic children. The Family Planning Association of Iran is probably the largest while numerous small NGOs are active in the area of drug prevention and supporting people with HIV/AIDS. The semi-military youth organization of Basij affiliated with the Revolutionary Guards Army is also an important health-related NGO because of its enormous contribution to the periodic mass mobilization in support of public health interventions like immunization campaigns. Likewise, although not organized as an NGO, the enormous corps of the Women Health Volunteers may

also be viewed as an NGO. Due to the supportive stance on NGOs and other forms of civil society participation of the President Khatami, NGO movement has received a greater attention from the UN agencies over the past few years[7].

Discussion

While the civil society sector is a sizable force in a wide range of countries, there are considerable differences among countries. The civil society organization workforce in the developed countries is more than three times larger than that in the developing countries. The relatively limited presence of civil society organizations in the developing countries does not, of course, necessarily mean the absence of helping relationships in these countries.

Countries vary in the extent to which these organizations rely on paid as opposed to volunteer workers. Thus, while volunteers comprise 43 percent of the civil society workforce overall, reliance on volunteers varies considerably among countries-from a low of under 10 percent in Egypt to a high of over 75 percent in Sweden and Tanzania, and averages 38 percent among the countries we have examined. Surprisingly, however, no systematic difference exists between developed and developing countries along this dimension. Since the developed countries also have larger paid nonprofit employment, this suggests that the presence of paid nonprofit employment does not displace volunteers, as is sometimes alleged. This pattern reflects the long history of social movements in these countries coupled with the role that the state has assumed as both a provider and financier of social welfare services, something that is far less in evidence in other countries, including many so-called European "welfare states." To understand this more fully, it is useful to turn from this overview of the size of the civil society sector to an analysis of its composition[8-10]. Charitable organizations have vast experience in overcoming the difficulties associated with carrying out charitable work in distant lands. Some challenges are merely inconvenient: language barriers, cultural differences, technological limitations. Charitable organizations have successfully addressed these challenges through attention to procedures designed to reduce the risk that charitable assets would be used for non-charitable purposes[1].

In many low-income countries, NGOs support research activities and deliver basic health services in particular areas or among certain populations. Their effectiveness in establishing sustainable primary health care systems has been linked with promotion of community participation, having close links with the poor, being flexible and having committed staff.

The comparative advantage of NGOs might be assessed in terms of efficiency, innovation, quality of services, ability to mobilize resources, contribution to the sustainability of the local health system and coverage of grassroots communities[5,11].

Charitable organizations must exclusively pursue the charitable purposes for which they were organized and chartered. The mission of an organization defines its purpose, its program activities, its values and operations, and the measures of its success. Finally considering the successful pattern and strong points of the charities in other countries, especially Islamic countries, helps us to promote the status of charity service delivery to the community.

References

1. Buchanan R. Principles of International Charity Developed by the Treasury Guidelines Working Group of Charitable Sector Organizations and Advisors March 2005.Available at: www.ombwatch.org/npa/ Treasury%20Principles%20Final%20Document%20pdf
2. Palmer, N.; Mills, A.; Wadee, H.; Gilson, L.; Schneider, H. Policy and Practice:A new face for private providers in developing countries: what implications for public health? Bulletin of the World Health Organization 2003, 81 (4) : 292-297.
3. Lefton RB. Developing organizational charity-care policies and procedures. Healthc Financ Manage.2002Apr;56(4):52-7.
4. International Islamic Charitable organization (IICO). Available at: http://www.iico.org/home-page-eng/index-eng.htm
5. MERCER A, HOSSAIN KHAN M, DAULATUZZAMAN M, REID J. Effectiveness of an NGO primary health care programme in rural Bangladesh: evidence from the management information system. Health Policy Plan. 2004; 19(4):187-198.
6. The Palestinian Population. www.emro.who.int/mnh/whd/CountryProfile
7. Country Cooperation Strategy for World Health Organization and Islamic Republic of Iran.www.emro.who.int/iran/media/pdf/Iran-CCS.pdf
8. Salamon LM, Sokolowski SW.Global Civil Society An Overview. Hopkins Comparative Nonprofit Sector Project. Available at: www.jhu.edu/~ccss/pubs/pdf/globalciv.pdf
9. Reid EJ and Kerlin JA.International Understanding, International Development and Assistance,and International Affairs. Available at: www.urban.org/UploadedPDF/411276_nonprofit_subsector.pdf
10. Tuan T, Dung VT, Neu I, Dibley MJ. Comparative quality of private and public health services in rural Vietnam. Health Policy Plan.2005;20(5):319-27.
11. Porter JD,Ogden JA,Rao PV,Rajesh D,Buskade RA and Soutar D.Introducing operations research into management and policy practices of a NGO.a partnership between an Indian leprosy NGO and an international academic institution.Health Policy Plan.200;19:80-7.

Models and Systems of Elderly Care

A Comprehensive Review on Psychological Issues of Women in Pakistan

Author:
Mr Hamzullah KHANs
Final year MBBS
Khyber Medical College
Peshawar, Pakistan

Correspondence:
Room No.104, Qasim hall hostel,
Khyber Medical College,
Post office: Campus Branch, University of Peshawar,
Postal code: 25120, Peshawar, Pakistan.
Phone number: 0092-345-9283415
Email: hamza_kmc@yahoo.com

Introduction

In Pakistan, societal attitudes and norms, as well as cultural practices (Karo Kari, exchange marriages, dowry, etc.), play a vital role in women's mental health[1]. The religious and ethnic conflicts, along with the dehumanizing attitudes towards women, the extended family system, role of in-laws in daily lives of women, represent major issues and stressors. Such practices in Pakistan have created the extreme marginalisation of women in numerous spheres of life, which has had an adverse psychological impact. Violence against women has become one of the acceptable means whereby men exercise their culturally constructed right to control women. Still, compared to other South Asian countries, Pakistani women are relatively better off than their counterparts[2]. Violence against women is very common in Pakistan. The violation of women's rights, the discrimination and injustice are obvious in many cases. A United Nations research study found that 50% of the women in Pakistan are physically battered and 90% are mentally and verbally abused by their men. A study by Women's Division on "Battered Housewives in Pakistan" reveals that domestic violence takes place in approximately 80% of the households. More recently the Human Rights Commission report states that 400 cases of domestic violence are reported each year and half of the victims die[3].

In Balochistan and Sindh provinces, Karo Kari is practiced openly. A woman suspected of immorality is declared a Kari while the Karo is a man declared to be her lover. A woman suspected of adultery or infidelity is liable to face the death penalty at the hands of her husband or in-laws. Usually the killer goes scot-free as he is regarded to have committed the crime in order to retrieve the lost family honour, which a woman is expected to uphold at all costs[4]. South Asian people in the UK under-utilize health services compared with White people. Also, where services are accessed, they may not adequately meet cultural and religious needs. In exploring the relationship between the cultural and religious beliefs of South Asian service users about perceptions, beliefs about aetiology, cause and treatment of mental illness, past studies have illustrated a wide range of expectations, experiences, beliefs and attitudes[5].

World wide the previous three decades witnessed great advances in female betterment covering all aspects of life and yet they continue leading complexly difficult lives. The cause of female suffering can be grouped under the heading "Contradictory Expectations"

Globalization and international capitalism portray the pathological difference between the first world woman's material comforts and the third world woman's wide spread exploitation. Whereas the former is coaxed into spending atrocious amounts "out of loathing for their bodies" the latter are sometimes "bought and sold, beaten and mutilated, even killed with impunity and social approval, disposed and disinherited despite legal safeguards[6]".Analyzing the scenario of female status in Pakistan and the consequential effects on their mental health, one finds a marked diversity in the lives of the urban and rural women, be it their identity, self-image, political awareness, freedom of expression or social status[2].

Rapid urbanization, impact of information explosion, along with increasing literacy rates, job opportunities and programs for women's empowerment both at government and NGO levels has had a positive impact on the lives of urban Pakistani women, placing them almost at par with women of the developed countries. Yet keeping in touch with their culture and tradition they uphold their social values rigidly, synchronizing between the cultural,

religious, and modern socio- economic needs and the intellectual and social demands of time. Despite the many irritants and constraints both at home and the societal level, where they are still not ready to accept woman-empowerment, the urban womeen strives to achieve their goals. Understandably in the absence of such hindrances the urban woman would have realized her inherent potential and personality strengths in a more positive, productive and balanced manner-yet the struggle goes on[7].

Factors Contributing to Psychological Issues of Women

Factors contributing to such doubts include societal and family pressures. Following are only a few to illustrate the point.

• Societal Pressures

1. Restricted mobility for women, affects their education and work / job opportunities; this adds to the already fewer educational facilities for women.
2. Concept of "chadar and chardiwari", veil and being restricted to the safety of the home has further suppressed women.
3. Rampant violence in society, ethnic riots and political unrest has clearly affected the Pakistan woman's progress.
4. Sexual harassment at home, at work and society has reached its peak for lack of awareness or denial of its existence, further confining women.
5. Violence like rape, assault, acid burns and Karo Kari further adds to their restrictions thereby lowering prospects of women's empowerment in society.

• Family Pressures

1. Birth of a baby boy is rejoiced and celebrated while a baby girl is mourned resulting in guilt and despair in many families.
2. Boys are given priority over girls for better food, care and education. Subservient behavior is promoted in females.
3. Early marriage (child-brides), Watta Satta (exchange marriages), Dowry and Walwar (bride price).
4. Divorcees and widows are isolated and considered "bad omens" and are victims of both male and female rejection especially in villages.
5. Marriage quite often leads to wife battering, conflict with spouse, conflict with in laws, dowry deaths, stove burns, suicide/homicide and acid burns to disfigure women in revenge.
6. Issues related to fertility and second marriage.

• Health Care Facilities

1. Poor treatment leading to high maternal mortality rate (MMR) and infant mortality rate(IMR)
2. Women have no control over contraception or the number of children they want.
3. Anemia and poor physical health due to poor nutrition, multiple births, miscarriages etc.

• Lack of Social Support

1. Nuclear families in urban families lack extended family support.
2. At government level there are no community social support centers or day care centers for children of working mothers. Dual career families suffer the most[8,9].

The psycho-social stressors of Pakistani women are present throughout their life-cycle from childhood to adolescence, adulthood, middle age and old age. The following table[10] illustrates the same:

Table : Psycho-social Stress in Pakistani Women

Life Cycle Stages	Biological Stresses	Psycho-social stressors
Childhood (0-12 years)	• Low nutritional status • Low opportunities for exercise	• Discriminatory attitude as compared to male • Low opportunities for education and growth
Early adolescence (12-15 years)	Menarche/ puberty	• Increased responsibilities at home • Further limitations of options • Targets of sexual harassment • 'marriage' & issues around it e.g. selection or rejection • discrimination by parents in education and social life
Late adolescence(15-18 years)		• Problems of identity / self image • Career choice / marriage issues • Gender differences in rearing by parents • Restriction in mobility

Early adulthood	Pregnancy	• Target of emotional / physical abuse by husbands plus / or in-laws • The more the number of children the worse the stress • Multiple responsibilities; wife, mother, daughter-in-law
Mature adulthood (30-45 years)	Multiple pregnancies or infertility	• Low control over pregnancies / contraception • Unacknowledged housework conflict between 'work' plus 'family'
Middle age (45-60 years)	Menopause	• Pervasive powerlessness plus low self esteem • Children leaving home 'empty nestsyndrome'
Old age (above 60 years)		• Bereavement • Old age depression • Isolation if living alone • No social support at government level (like old peoples homes, social security etc.)

Psychological Problems in Women Physicians in Pakistan

Women practicing medicine are known to have high-stress lifestyles. Medicine is an inherently stressful profession with long hours, pressing clinical problems, ethical dilemmas, difficult patients and conflicting demands. Several studies have reported elevated rates of depression, anxiety, marital problems and higher suicide and addiction rates among physicians compared to other professionals[11]. There is little published work quantifying either the effects of stress on doctors or the results of interventions designed to reduce stress. Grol demonstrated poor clinical performance in those doctors with negative feelings of tension, lack of time and frustration as evidenced by having a high prescription rate and give little explanation to the patients[4]. The effects of stress on practice are evidenced as increased errors in prescribing, increased staff turnover, limited team working, more patient's complaints, poor time- keeping and sickness absence. Stressed GPs may develop problems in their relationships with their partners and family at home, these include becoming uncommunicative at home or work and more withdrawn and isolated[12].

Psychological Problem, Anxiety and Depression in Non-Working Women with Reference to their Education, Family System and Number of Children in Pakistan

There is anecdotal evidence that housewives frequently complain about the monotony of their lives. They feel that they have to look after children and do the housework and they do not have time for themselves. Compared to the working women, their social environment is limited. Their husbands are the only ones to appreciate their intense efforts they make for their homes. A woman, for instance, with six children and a husband, and with no help from others and no money for the most costly labor-saving devices, simply can not organize her necessary duties so that she will have leisure for pleasures and activities outside the daily routine. In such a house the most modest requirements for food, shelter, and clothing become a driving force that pushes aside relentlessly any irrelevant longing. The working women, however, have the chance of being appreciated by the society and behave independently and earn money. On the other hand, many working women find that children provide a common focus of interest for them and their husbands and many of them feel that the time devoted to children resulted in less sharing and companionship and less spontaneity in the marital relationship[13,14].

A study showed that both working and non-working women living in a joint family system were more frequently diagnosed with anxiety; but that association was not statistically significant.

A highly significant association was observed between anxiety in women and the number of their children. This study showed that majority of non-working women (79.5%) diagnosed with anxiety had more than three children as compared to working women (11.1%)[15].

Anxieties in Pregnant Women of Pakistan

Pregnancy has dramatic emotional and psychological consequences for the individual. There is evidence of increased incidence of anxiety and depression in pregnancy. Mental disorders are more common in pregnant women who have a past history of psychiatric illness, family psychiatric history, past obstetric/gynaecological complications, caesarean section and those who lack marital, family or social support[16].
A large number of studies have reported prevalence of anxiety and depression in pregnancy from different parts of the world. There are few studies on this topic from Pakistan. It is important to estimate the prevalence of anxiety and depression in pregnant women in Pakistan because it has effects on both mother and child.

The aims of the present study were as follows:

To investigate the prevalence of anxiety and depression in pregnant females presenting in the antenatal clinic of a teaching hospital

To find out risk factors associated with anxiety and depression in the above group.

To assess the relationship of different demographic variables with anxiety and depression in the above group[17,18].

Marital Problems and Their effect on Women's Mental Health

The concept of marital satisfaction is an important area of research in the context of marriage and family relationships. This has not been previously examined in Pakistan, a conservative patriarchal Islamic country, where studies examining psychiatric morbidity have shown marital problems as contributing to Common Mental Disorders (CMDs).

Young married women under the age of 35 years appear to have a higher prevalence of CMDs than older married women. In this pilot study, using both a quantitative and a qualitative approach, we examined the construct of marital satisfaction and tested the applicability of marital satisfaction scales developed in the West for use in Pakistan. The results indicate that, contrary to cultural beliefs regarding marriage, most women expressed the need to be satisfied within marriage. The fear of hurting or annoying their parents prevented many women from openly expressing their opinion in the choice of husband or unhappiness in their marriage. Pakistani women tend to see marriage as a social and familial obligation requiring them to be prepared to adjust as the man seldom does. The construct of marital satisfaction is a viable concept for study and research in Pakistan, and there is need for further research in this area[19].

From the above discussion we concluded that factors positively associated with anxiety and depressive disorders in women of Peshawar were mainly social problems, cultural taboos. The religious and ethnic conflicts, along with the dehumanizing attitudes towards women, the extended family system, role of in-laws in daily lives of women, represent major issues and stressors. Other factors are female sex, middle age, low level of education, financial difficulty, being a housewife, and relationship problems.

References

1. National Commission on the Status of Women. Report of the status on women in Pakistan. Islamabad: 1997.
2. Niaz U. Human rights abuse in family. Journal of Pakistan Association of Women's Studies. 1994; 3:33-41.
3. Khan MM, Islam S, Kundi AK. Para suicide in Pakistan: an experience at University Hospital. Acta Psychiatr Scand. 1996; 93:264-267.
4. Population Division, Department of Economic and Social Affairs, United Nations Secretariat. U.N. The world at six billion (ESA/P/WP.154). Part 2-Table 5-8. New York: UN, 1999: 12-22.
5. Hussain F. Depression in South Asian Women Living in the UK: A Review of the Literature with Implications for Service Provision. Transcultural Psychiatry, Vol. 41, No. 2, 253-270 (2004).
6. Greer, Germaine. "The Whole Woman" Published, Anchor - a division of Transworld Publishers 2000.
7. Niaz U. A monograph on womens mental health "A millennium Publication" A Publication of Pakistan Psychiatric Society 2000.
8. Access & Usage of Basic Health services in Pakistan, Federal Bureau of statistics Islamabad 1997.
9. Haskell, Lori & Melani Randall. The policy of womens safety: sexual violence, womens fears & the public/ private split. Resources for feminist research Vol. 26, No. 3/4;1999.
10. Niaz U. Overview of Women's Mental health In Pakistan. Pak J Med Sci, 2001; 17(4): 203-209.
11. Pilowski L, O'Sullivan, G. Mental illness in doctors. BMJ 1989; 298:269.
12. Grol R, Mokkink H, Smits A, Van Eijk J, Beek M, Mesker P, Mesker-Niesten J. Work satisfaction of general practitioners and the quality of patient care. Fam Pract 1985; 2(3): 128-35.
13. Nathawat SS, Mathur A. "Marital adjustment and subjective well-being in Indian educated housewives and working women."
14. J Psychol 1993; 127(3): 353-8. Rani G & Yadav A. Anxiety level among working women. Jour Personality & Clinical Studies, 2000; 16(1): 63-7.
15. Iqbal A, Nadeem R, Fatima N.Anxiety in non-working women with reference to their education, family system and number of children. Pak J Med Sci, 2004; 20(4):345-348.
16. Gelder M, Mayou R, Cowen P. Shorter Oxford textbook of psychiatry. Oxford. Oxford University Press. 2001: 497-503.
17. Niaz S, Izhar N, Bhatti MR. Anxiety and depression in pregnant women presenting in the OPD of a teaching hospital. Pak J Med Sci, 2004;20(2): 117-119.
18. World Health Organisation The ICD 10 classification of mental and behavioural disorders. 1992; World Health Organisation Geneva.
19. Qadir F, Silva PD, Prince M, Khan M. Marital satisfaction in Pakistan: A pilot investigation. Routledge, part of the Taylor & Francis Group,2005;Volume 20, Number 2 : 195 - 209

Models and Systems of Elderly Care

Independent Grandmothers in An Iranian Village

Author:
Mary Elaine Hegland, Santa Clara University

In "Aliabad," a large village in southwestern Iran, older widowed women are often deciding to live by themselves in their own homes rather than living with sons as was generally the case until recently. With research data collected in Aliabad, interviewing and participant observation in other nearby villages and Shiraz, and extensive fieldwork among Iranian grandparents in California's Santa Clara Valley, I have been investigating this fast growing phenomenon of independent grandmothers.

Previously, I had lived in Iran for about a total of four years, a year and a half in this same village. I was able to return to Aliabad for two weeks in September 2003, four weeks in July and August 2004, and three months in December 2005 to March 2006, and am thus able to compare conditions for widowed Aliabad grandmothers a quarter of a century ago with their current situations.

Aliabad in 1978/1979

In June 1978, Aliabad was a village of about 3,000, about half an hour by bus away from the outskirts of Shiraz, capitol of Fars Province. Not long before 1978, almost all village men had been either agriculturalists or shopkeepers and traders in outlying areas, or both, or worked in crafts or shops in the village. By 1978, some men were beginning to work in factories built between Aliabad and Shiraz, construction companies, or in service jobs in Shiraz.

Most people lived within the old village walls, in mud brick homes covered with a mixture of mud and chopped straw to protect the mud brick from rain. Although better off than people in many other villages in the area, partly because of the proximity to Shiraz so that men could commute to a job in the city, villagers lived at a very simple level. Rooms, often in two layers, the upper for people and the lower for animals, were arranged around a central courtyard with a dirt floor. Most village men remained illiterate, and even more women had not been able to attend school, although in 1978 and 1979, most boys and girls attended school for a few years. Girls were generally kept at home after puberty, and were married young, at 14 or 16 or even earlier.

Generally, relatives lived in the rooms of a courtyard, with at least one room reserved for each married couple. When parents arranged a wife for their son, the young couple most often moved into a room in the parental home or courtyard. A new bride was expected to be even more home-bound and modest than older women, and should obtain permission from her husband and in-laws for any actions or forays outside of the home. With the groom was away at work, the mother-in-law kept close watch on her daughter-in-law, and directed her labor and activities. In 1978/1979, no Aliabad widows lived on their own. Rather, they lived with a son and maintained a relatively strong presence, at least as long as they were physically and mentally capable.

Aliabad in 2003/2004/2005/2006

Returning to Aliabad in September 2003, 24 years later, I was faced with dramatic changes. With money from land sales, jobs, and government loans, most villagers had left the old village to build urban-style fired brick homes with a bricked courtyard, within high walls on new streets expanding out from the old village areas. The old village walls had disappeared. Very few men in the village practice agriculture or animal husbandry. Rather, they have government jobs, ferry passengers in their cars between Aliabad and Shiraz, work in factories or construction, or have or work in shops and little businesses in Shiraz. Shops and businesses, some in the process of construction, and even a gasoline station, line the highway passing through the village, and even stretch out much of the way along village land toward Shiraz. The village population has expanded from about 3,000 to some 7,000 as people from outlying areas move in to take advantage of the many construction jobs and work in services and shops, more than making up for those villages who have moved to Shiraz or even elsewhere.

In addition to new homes, complete with modern kitchens and shower rooms, some ceilings and arches are decorated with plaster or intricate mirror work, people now dress and eat far better. Homes are larger, with several rooms, and most often house a nuclear family only. Girls can attend the local junior high school, or guidance school, and then can take the bus into Shiraz for high school. As elsewhere in Iran, more females than males are successful in passing the difficult exams to gain admittance to a

university. A number of village girls are attending universities in cities of the southwest region of Iran. Several, especially those who have moved into Shiraz, even attend university in Tehran. Age of marriage for girls has gone up dramatically, and brides practice birth control, putting off children and even then having only one, two, or at most three children.

Young women may refuse the men whom their parents have chosen for them to marry. A young wife does not want to be under the thumb of her mother-in-law but rather aims, usually quite successfully, to keep her husband's attention, affection, and resources for herself. Instead of the avoidance which husband and wife practiced in front of others in the past, a couple may be openly affection are with each other.

Sons' wives have become much more independent of their mothers-in-law. Instead of living with their mothers-in-law, being almost totally under their control, watched very carefully by them, and ordered to perform work by them, daughters-in-law live separately, do not work for their mothers-in-law, and do not obey them. They spend their time with their children, husbands, and own relatives. They socialize with their mothers-in-law only to the extent that they like them and enjoy their company.

These many constellations of change, related to the process of change and transformation from pre-modern to modern social and cultural organization and dynamics, have had a powerful effect on the living situations and attitudes of Aliabad mothers and mothers-in-law. Many of them have become independent grandmothers.

Independent Village Grandmothers

During the 2003, 2004, and 2005-6 visits to Aliabad, I was amazed to find out that many older widows live by themselves. I taped interviews, guided discussions, collected more than 40 cases studies of grandmothers who live by themselves, and spoke with many younger people as well. From this material, some trends in family organization and dynamics become apparent.

These grandmothers are not as controlled by family pressures to live with sons, in order to be under the guardianship of a related male. They live in their own homes but often visit very frequently in the homes of their children and other relatives, staying over night or even for long periods of time. Three main factors influence this trend, making it less likely or attractive for grandmothers to live with their children.

A main reason why many Aliabad grandmothers are able to live on their own is the existence of sufficient financial resources. Women can keep their own homes and live off rent money, husbands' pensions, financial assistance from children, income from property, and/or assistance from the local branch of a welfare agency. Their children, also relatively financially well-off because of businesses, salaries, loans, or sale of land, are able to have separate homes and do not need to live in the parental home as they did in earlier years.

Some grandmothers say they want to live in their own homes and feel as if they are running their own lives. "They do not have the patience for daughters-in-law and children," someone said. "Some really like to be separate, they cook and shop for themselves."

Changes in family hierarchy and dynamics and in living style among the younger generation, especially in Shiraz but also in Aliabad, often make it uncomfortable for the older people to live with their children and grandchildren. Decades ago there was not such rapid change. Young people and the older generation lived pretty much the same way. Now most often the older grandmothers are illiterate whereas the daughters-in-law have gone to high school or more. Their different ways of thinking makes it hard for them to live together.

The marital couple relationship and nuclear family have grown more important. Less time and fewer resources therefore are available for in-laws and extended family. Often the daughters-in-law and grandchildren do not treat the grandparents with the deference expected, so it is less pleasant for the older people to be around the younger ones for long periods of time. Daughters-in-law might prepare unfamiliar foods such as sandwiches and pizza for children, especially in Shiraz. Because of changes in life style, the older women do not feel very comfortable about the thought of living in their sons' homes.

A third reason why grandmothers may live alone is related to the wishes of daughters-in-law. Some grandmothers do not want to live alone, but the daughters-in-law do not want them.

Brides are not as much subject to the power and authority of their in-laws as they had been 25 years ago. Brides-to-be and their families have become very demanding even in the village, people told me, about the house and car and furnishings which they expected to be ready for the brides before they would move in. They and their families insist on a separate home.

"They do not like to live alone, but their children can not live with them. Many of their daughters-in-law, (arus) do not like to live with them. The sons go off and live with themselves comfortably, and leave them. They are unhappy. They like to have someone to talk with."

One woman said, "There are many, many old women who live alone in the village. They have plenty of time to tell anyone about their problems, so they will feel better (delesh baz misheh). They are alone."

Often Aliabad grandmothers have mixed feelings about their independent living status. One day, my friend Esmat and I went into Shiraz, invited by her close friend Fatemeh, who lives in a small apartment near Shah Cheragh Shrine. I asked about their lives as mothers and grandmothers who live in their own homes.

Mary: Why don't you live with your children?

Fatemeh: I want to live for myself. I want to go and see them only, and stay with them for 1 or 2 nights. If my son would build a house and have one level for me, I would go, but otherwise I don't want to live with them.

Mary: Why not?

Fatemeh: I think I would be a bother for them, an interruption for them. There would be no freedom, not for them, not for me. (Now) if I am tired, I go and rest. If I want tea, I make tea. If I were with them, if they made tea, I would have it. If they didn't, I wouldn't have tea. Now if I am hungry, I eat. With her (her daughter), we have to wait until her husband comes home at 6 to put out the tablecloth, even if I am hungry.

They (daughters-in-law) don't like the mother-in-law. They like to live separately and go where ever they want. They want their own car. Daughters-in-law prefer to visit with their own families, with their own mothers and their own sisters.

Then Esmat spoke up.
I don't want to live with my children. I want to be independent (mostaqel). If I live with my children, and the authority, permission, rights, discretion (ekhtiyar) will be in their hands, I won't have the permission to go around and see you, and you (nodding to each of us in turn). She (the mother or mother-in-law) knows how to do things better than they do, but if she is at their houses, they say, oh, she is an old women, she can't do this, she can't do that.

The day before this conversation, Fatemeh had talked about how there isn't much to do; it is hard to go out by yourself; and she is tired of being alone and that is why she spends most of her time with her children or others. Esmat had agreed that it is difficult for a woman to live alone, particularly under the existing confining social conditions for women. They both recognized the challenges of maintaining separate residency and thus independence. However, especially considering the attitudes of daughters-in-law and the younger generation, they prefer to visit rather than reside in the homes of children.

Several other grandmothers made comments about the loneliness of living alone, and about how they missed having a busy, crowded household as they had when the children were still living with them. One elderly woman told me her nerves are bad. I asked her why. "Why shouldn't my nerves be bad?" she responded. "Before, I had four of my children around me, and now I am alone."

Although these grandmothers speak about wanting to manage their own lives and maintain their own schedules, they have made the decision to live separately from their children, in spite of the drawbacks and loneliness, based on a realistic evaluation of current conditions and relationships. Lacking inherited cultural scripts for independent grandmother lives, they are making the best of it and trying to see some advantages and opportunities in overwhelming social change. They are pioneering the effort to improvise new lives and new scripts for independent Iranian village grandmothers.

Education and Training

Case report: Hypothyroidism in Elderly

Author:
Dr.Nehal Shams. B.Sc (USA). MB.MRCP (UK) .DME
Dr. Safwat Hamad
Consultant physician and Geriatrician Medical Registrar
Portiuncula Hospital
Rep. of Ireland

Introduction

We report a rare case of an elderly lady who presented with severe dementia (mini-mental score of 8/30), with dramatic improvement, following replacement of thyroid hormone. Mini-mental score of 30/30 on discharge.

The History

A 65 year old female, was sent by her G.P with one week history of cough, wheeze, visual hallucinations and increasing confusion.. She reported seeing objects on her body and floor. She had a past medical history of controlled Atrial fibrillation, impaired renal function, mild cognitive impairment, hypertension and coronary artery bypass graft. She was on Risperidone 0.5 mg daily, Quetiapine 25 mg, Digoxin 0.125 mg daily, Clopidrogil 75 mg daily, Warfarin, Pravastatin 40 mg daily, Donepezil 10 mg and Sertraline 100 mg.

She was comfortable at rest and her vital signs were stable. Examinations, showed wheeze and scattered crepitations in the mid and lower zone of the right lung. Pulse 55 irregular, normal JVP, heart sounds and no peripheral oedema. She was disoriented in time, place, with mini-mental state examination score of 8 /30.

She had ECG, chest X-ray and urinalysis in casualty and all were normal, apart from Atrial fibrillation with a heart rate of 55/minute. Full blood count, urea & electrolytes, inflammatory markers, B12, folate and liver function test were all normal.

An initial diagnosis of lower respiratory tract infection and medication induced hallucinations was made. She was started on antibiotic, Sertraline and Resperidone were withheld. But the hallucinations persisted .She had episodes of laughing and uncontrolled crying. She also had episodes of confusion and agitation and physically hitting family members. There were moments when she was lucid. Her speech remained clear. She was mobile but unsteady with broad-based gait. According to family, she was a quiet and shy person, there was no history of weight gain or loss and no history of constipation. She had bradycardia but we felt that could be related to the B blocker. We stopped the drug but she remained bradycardic. She had CT Brain, which was normal.

Over the next five days she continued to deteriorate and became sleepier and developed mild facial puffiness .At this stage, a Thyroid function test (TFT) was ordered. We routinely do TFT in this hospital for dementia screen but because she had a previous history of dementia, this was not done. Thyroid function test showed TSH of more than 100 (0.35-5.5), free T4 of 3.3 (11.5-23.) The treatment plan was discussed with the Endocrinologist, following which, the patient was started on intravenous triiodthyronine, intravenous hydrocortisone and oral Levothyroxine. As she has history of heart disease, the dose of oral Levothyroxine was started slowly and gradually increased. In the next five days, the patient showed dramatic response to thyroid hormone with improvement in all symptoms.

The confusion, agitation and hallucination all disappeared. We stopped her Donipezil, as we feel that she may have been suffering from hypothyroid for some time which may have been misdiagnosed as dementia. She was discharged after two weeks of treatment. The T3 was stopped and oral Levothyroxine was continued. Her mini-mental score was 30/30 on discharge. We will review her in the OPD and intend to repeat her TFT in four weeks.

Discussion:

Hypothyroidism is a clinical disease that is characterized by decreased thyroxin production. The prevalence of hypothyroidism increases with age, ranging from 0.5% to 6% for overt hypothyroidism and from 4- 15% for sub-clinical hypothyroidism. It is more frequent in elderly Caucasian women, and is more commonly observed in hospitalised, as compared to free-living, subjects.

Causes:

The most common cause is autoimmune thyroid disease. Treatment of Grave's disease is another common cause of

hypothyroidism in the elderly population. Iodine-containing drugs such as radiographic contrast agents and the anti-arrhythmic amiodarone may precipitate the development of hypothyroidism. Similarly recombinant interleukin-2A16 and recombinant interferon-alpha17 may precipitate hypothyroidism especially in patients with underlying autoimmune thyroiditis. A significant number of patients receiving long-term lithium therapy develop an elevation of TSH, a response to the inhibition of thyroid hormone release by this drug, and some develop overt hypothyroidism. Hypothyroidism caused by pituitary or hypothalamic disease is very rare and is usually the result of tumours or surgery

Effect of age on the thyroid gland:

As a person ages, the structure of the thyroid gland changes. Some studies have shown an increase and others a decrease in the size of the gland with aging. This discrepancy is probably related to dietary iodine intake. At the same time, however, there is a decrease in the number and size of the follicles as well as in colloid content. Histopathologic examination shows lymphocytic infiltration and fibrosis of the connective tissue. The gland also becomes increasingly nodular with age.

In spite of these structural changes, results of thyroid function tests are normal in most patients. Serum levels of free thyroxin (T4) remain constant with aging, because a decline in production is offset by slower metabolism. Although initial studies in heterogeneous populations suggested a decline in triiodothyronine (T3) levels with aging, later studies in selected healthy persons showed that the levels are unaffected. Thyrotropin (i.e.TSH) levels typically remain normal, except for a mild decrease in extreme senescence (i.e. octogenarians). A blunting of diurnal variation in thyrotropin levels and the thyrotropin response to thyrotropin-releasing hormone may occur, especially in elderly men, but this effect is rarely clinically significant. Some studies also have shown an elevation in thyroid auto antibodies with aging, but the increase seems to be the effect of age-associated disease rather than aging per se.

Symptoms and signs of hypothyroidism in elderly:

Older patients had fewer symptoms, and some of the classic signs (e.g. cold intolerance, weight gain) were often absent. Moreover, the common clinical features of hypothyroidism (e.g. fatigue, constipation, cognitive loss) are often attributed to normal aging. These factors, along with the fact that hypothyroidism has an insidious onset and affects multiple organ systems, may cause considerable delay and difficulty in diagnosis. Therefore, it is important to have a high index of suspicion and a low threshold for screening for thyroid dysfunction in elderly patients who present with vague, non-specific symptoms.

Atypical signs and symptoms in elderly patients:
Confusion
Behavioural changes
Macrocytic anaemia
Peripheral neuropathy
Dementia-like behaviour
Memory impairment
Myopathy
Depressed affect
Muscle weakness

Diagnosis:

The single best diagnostic test for primary hypothyroidism is an increased serum thyroid stimulating hormone concentration, but, compared to young hypothyroid patients, old individuals with primary hypothyroidism may have significantly lower basal serum thyroid-stimulating hormone levels. Test for anti-thyroid antibody help to identify patients with autoimmune thyroiditis, but don't provide direct information on thyroid function and an hypo-echogenic pattern of the thyroid by ultra-sonography helps in identifying auto-immune thyroiditis.

Myxoedema coma:

Is defined as severe hypothyroidism leading to decreased mental status, hypothermia, and other symptoms. It is a medical emergency with a high mortality rate. Fortunately, it is now a rare presentation of hypothyroidism, probably because of earlier diagnosis. The demographics of patients who develop myxoedema coma are those of hypothyroidism in general, with older women being most often affected. Myxoedema coma can result from any of the usual causes of hypothyroidism, particularly chronic autoimmune thyroiditis, because of its often-insidious course compared with post-surgical or -ablative hypothyroidism. It can occur in patients with secondary hypothyroidism, and there are case reports of its occurrence in patients with lithium- or amiodarone-induced hypothyroidism.

The hallmarks of myxoedema coma are decreased mental status and hypothermia, but hypotension, bradycardia, hyponatremia, hypoglycaemia, and hypoventilation are often present as well. The possibility of a precipitating infection or other acute illness should always be considered; it is important to appreciate, however, that the patient may not have a febrile response to infection.

Despite the name, myxoedema coma, patients frequently do not present in coma, but do manifest lesser degrees of altered consciousness. This usually takes the form of confusion with lethargy and obtundation. Alternatively,

a more activated presentation may occur with prominent psychotic features, so-called myxoedema madness. Untreated, patients will progress to coma.

Treatment:

The goal of therapy is restoration of the euthyroid state, which can be readily accomplished in almost all patients by oral administration of synthetic thyroxin (T4). However, some patients may benefit from a combination of T4 and T3. The average daily replacement dose of L-Thyroxin (L-T4) in adults is 1.6 mcg/kg, but elderly hypothyroid patients require a dose of 20-30% lower, and they display a narrow therapeutic range and require close monitoring of serum thyroid stimulating hormone to avoid over-treatment. It is important to "start low and go slow," because the half-life of circulating levels of T4 increases with age.

L-T4 therapy should be initiated with a dose of 12.5-25 mcg/day, followed by careful increments of 12.5-25 mcg/day every 4-8 weeks, to reach the full replacement dose in several months. Particular attention should be paid in patients with co-existent or suspected cardiac disease, since L-T4 substitution may precipitate angina or myocardial infarction. On the other hand, L-T4 substitution ameliorates reversible hypothyroid heart dysfunction and produces beneficial effects on hyperlipidaemia.

Myxoedema coma - Patients with myxoedema coma should be treated aggressively, because the mortality rate approaches 80 percent. If the diagnosis is suspected, a blood sample should be drawn for measurement of serum T4, TSH, and cortisol before therapy with a glucocorticoid and thyroid hormone, which are then given immediately, before laboratory confirmation of the diagnosis. The serum T4 concentration is usually very low.

The serum TSH concentration may be high, indicating primary hypothyroidism, or low, normal, or slightly high, indicating central hypothyroidism.

Whether patients with myxoedema coma should be treated with T4 or T3, or both, is controversial. Some experts favour administration of T3, while others favour T4, preferring that T3 production be governed by the activity of 5'-deiodinase in the patient. What is important is that a substantial dose of thyroid hormone be given, even though there may be some risk of precipitating a cardiac arrhythmia or myocardial infarction.

Combined therapy is recommend in most patients. An initial dose of 200 to 300 mcg T4 intravenously, depending upon body weight, followed by daily intravenous doses of 50 to 100 mcg until the patient can take T4 orally. T3 is given intravenously at the same time; the initial dose is 5 to 20 mcg, followed by 2.5 to 10 mcg every eight hours depending upon the patient's age and coexisting cardiovascular disease. T3 is continued if there is clinical improvement and the patient is stable.

Supportive measures are extremely important, including mechanical ventilation, appropriate fluid replacement, and correction of hyponatremia and hypothermia. In addition, there is often an associated illness that must be treated, such as infection, or gastrointestinal bleeding. Until coexisting adrenal insufficiency can be excluded, the patient should be given high-dose glucocorticoid therapy (hydrocortisone 100 mg intravenously every eight to twelve hours for two days, then lower doses).

References

1. Flynn, RWV, MacDonald, TM, Jung, RT, et al. Mortality and vascular outcomes in patients treated for thyroid dysfunction. J Clin Endocrinol Metab 2006; 91:2159.
2. Lamson, MJ, Pamplin, CL, Rolleri, RL, et al. Quantitation of a substantial reduction in levothyroxine absorption by food. Thyroid 2004; 14:876.
3. Oppenheimer, JH, Braverman, LE, Toft, AD, et al. Thyroid hormone treatment: when and what? J Clin Endocrinol Metab 1995; 80:2873.
4. Dong, BJ, Hauck, WW, Gambertoglio, JG, et al. Bioequivalence of generic and brand-name levothyroxine products in the treatment of hypothyroidism. JAMA 1997; 277:1205.
5. Blakesley, V, Awni, W, Locke, C, et al. Are bioequivalence studies of levothyroxine sodium formulations in euthyroid volunteers reliable?. Thyroid 2004; 14:191.
6. Joint statement on the U.S. Food and Drug Administration's decision regarding bioequivalence of levothyroxine sodium. Thyroid 2004; 14:486.
7. Denham MJ, Wills EJ. A clinico-pathological survey of thyroid gland in old age. Gerontology 1980;26:160.
8. P R Rizzolo, "Thyroid disease," in Primary Care Geriatrics: A Case-based Approach, third ed, R J Ham, P D Sloane, eds (St Louis: Mosby-Year Book, 1997) 449.
9. Rizzolo, "Thyroid disease," 447-455; R S Watts, "Hypothyroidism," in Saunders Manual of Medical Practice, ed R E Rakel (Philadelphia: W B Saunders, 1996) 635-641.
10. Oxford Text book of endocrinology and diabetes march 2002.