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EDITORIAL

Cultural aspects of caregiver burden in psychiatric disorders

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Abstract

Caring for a mentally ill family member is well known to be mostly a stressful, distressing and burdensome experience. The dominant model for examining the process of caregiving has been the stress-appraisal-coping paradigm, in which interactions between stressors, appraisals, coping, and various mediators produce the eventual outcomes in terms of distress or well-being among caregivers. Ethnic and cultural factors have traditionally received the least research attention as mediators of the caregiving process. However, a large body of accumulated research evidence has clearly demonstrated that culturally-defined values, norms, and roles are among the major determinants of the caregiving experience. This research is based mainly on cross-cultural comparisons between caregivers of minority ethnic groups residing in the West and the native Caucasian population. It has been supplemented, to a limited extent, by research carried out among caregivers belonging to different cultures and residing in their countries of origin. Most of this research has been carried out among caregivers of elderly people with dementia; other psychiatric disorders such as schizophrenia have received much less attention. Results of this research have documented important differences in caregiving experiences and outcomes across cultural and ethnic groups. Cultural factors which could mediate these differences have been identified, and theories, which could provide a coherent framework to understand these differences, proposed. Though limited by methodological difficulties, this research has provided important insights into the impact of cultural and ethnic factors on the whole spectrum of the caregiving experiences. An improved understanding of the area is, nevertheless, required because it will eventually help in devising appropriate ways to reduce burden and distress among caregivers from diverse ethnic and cultural groups.

Key words: Culture; Ethnicity; Caregiving; Caregiver-burden; Psychiatric disorders

Core tip: The cultural context shapes the entirety of the caregiving experience and its outcomes. Important differences have been identified in the extent of caregiving, caregiver burden and distress, attitudes and norms influencing caregiving, appraisal, coping, help-seeking, and social support, between caregivers belonging to diverse ethnic and cultural groups. Familial-cultural factors seem to be the principal determinants of caregiving outcomes, though they appear to influence burden and distress in complicated, and yet unclear ways. Since an understanding of the role of culture in caregiving is an essential first step towards helping lower burden among caregivers from different cultural and ethnic groups, more research is required in this area.

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CAREGIVING AND CAREGIVER-BURDEN

Caregiving has been defined as interactions, in which one

person is helping another on a regular basis with tasks, which are necessary for independent living[1]. Anyone who provides some assistance to another who is, in some degree, incapacitated and needs help is a caregiver[2]. Normal "care" changes into "caregiving" when it is out of synchrony with the appropriate stage of the lifecycle. For family caregivers, this change takes place when the reciprocity between family members is out of balance, such that the responsibilities and tasks of one party in a relationship go beyond those customarily expected. Family caregivers are often bound by kinship obligations to adopt certain duties and responsibilities that are far in excess of those normally associated with a family role at a particular stage[3]. In doing so, they may perceive considerable distress, have a poor quality of life and experience psychological morbidity. The consequences of being related to and caregiving in chronic mental illness can, thus, be roughly divided into the obligation to offer long-term extensive care, and the emotional distress and worries related to the life-situation of the patient. Such consequences of caregiving are usually referred to as caregiver-burden or burden of care. Caregiver-burden has, thus, been defined as the "the presence of problems, difficulties or adverse events which affect the life (lives) of the psychiatric patients' significant others (*e.g.*, members of the household and/or the family)"[4]. Research over the last five decades or so has clearly established that having a family member with mental illness can lead to high levels of distress and burden for caregivers. Research on caregiver burden has also identified the major areas of (objective) burden, namely adverse effects on the household routine including care of children, disruption of relations within and outside the family, restriction of leisure time activities of caregivers, the strains placed on family finances and employment, the difficulties in dealing with dysfunctional and problem behaviours faced by caregivers, and the impact on mental and physical well-being of the caregivers. The prevalence of subjective psychological distress, often referred to as subjective burden, has also been found to be very high[5-15].

Studies on caregiver-burden have also gradually moved beyond simple enumeration of the problems faced by caregivers on account of the patient's illness, to a consideration of the caregiving experience in its totality. The dominant model for examining the process of caregiving has been the stress-appraisal-coping paradigm of Lazarus and Folkman[16].

The "stress-appraisal-coping" theory suggests that the principal element of caregiving is an appraisal of its demands. The patient's illness and its impact on the caregiver are the main sources of stress. Coping with this stress is determined by how it is appraised. Mediators of the process include social, demographic and cultural factors, caregiver's personality traits, and the level of support they receive[17,18]. Thus, apart from identifying stressors, appraisal and coping as the central elements of the process of caregiving, this model also delineates certain mediators of this process. These mediators include illness variables (*e.g.*, diagnosis, severity, duration of illness, duration of remission, cost of treatment), the caregivers' socio-demographic and caregiving profile (*e.g.*, gender, education, relation with the patient, amount of time spent with patient), personality attributes (*e.g.*, neuroticism), socio-cultural factors which influence their attitudes towards caregiving, and the degree of social support available for the caregiver. These factors can influence appraisals, as well as the coping strategies adopted by the caregiver. Interactions between stressors, appraisals, coping, and the various mediators produce the eventual outcomes in terms of distress or well-being among caregivers[8,11].

Of all the mediators proposed by the "stress-appraisal-coping" model, ethnic and cultural factors have traditionally received the least research attention. This has changed over the last couple of decades or so with the advent of studies, which have clearly shown that culturally-defined values, norms, and roles are among the major determinants of the caregiving experience[10,11,13,19-31].

CULTURE, ETHNICITY AND CAREGIVING

Several strands of research can be identified in the broad area of the effects of culture and ethnicity on caregiver burden. The predominant methodology employed has been cross-cultural comparisons between caregivers of minority ethnic groups residing in Europe and the United States, and the native Caucasian population. The minority ethnic groups that have been the principal focus of such studies have included African-Americans, Afro-Caribbean, Latino or Hispanic groups, and Asian populations including Chinese, South Korean, Japanese and Indian caregivers[10-13,19-38]. This has been supplemented, to a limited extent, by research carried out among caregivers belonging to different cultures and residing in their countries of origin such as China, South Korea or India[12,13,28,30,39-45]. The examination of ethnic and cultural differences has encompassed virtually the whole spectrum of the caregiving experience. Consequently, it has investigated differences in caregiver burden and related factors such as service utilisation, cultural factors which could mediate these differences, and propounded theories, which could provide a coherent framework to understand these differences. Most of this research has been carried out among caregivers of elderly people with dementia or the physically frail elderly. Among "functional" psychiatric illnesses, schizophrenia has been the focus of research on ethnic or cultural differences in caregiving. Though the research data on schizophrenia appears to be qualitatively similar, the amount of data is, unfortunately, nowhere near the volume of research on dementia[12,46-48]. This is one significant deficiency of research in this area, which needs to be addressed.

CULTURAL DIFFERENCES IN CAREGIVING

There is a large body of comparative, cross-cultural re-

search evidence, which clearly indicates that caregiving experiences vary across cultural and ethnic groups. For the most part, this research suggests that caregivers from a number of ethnic minority groups differ from their Caucasian counterparts in several respects.

Although the evidence is somewhat equivocal, there seems to be a slightly higher prevalence of caregiving among Asian-Americans, African-Americans, and Latinos, than among non-Hispanic Caucasians. Moreover, when controlling for the levels of disability, minority caregivers tend to provide more direct and informal care than do Caucasian caregivers[49]. Caucasian caregivers are most likely to provide care for a spouse; Latinos are the most likely to provide care for a parent; and African Americans are the most likely to be caring for other family members or unrelated individuals[50]. In general caregivers belonging to the ethnic groups such as African-Americans, Afro-Caribbean, Latino or Hispanic groups, and Asian communities such as the Chinese, Korean, Japanese and Indian caregivers report lower levels of caregiving stress and burden[10-13,20-31,33,47,51,52]. They are generally more tolerant of the mentally ill relative[32]. Subjective perceptions of burden appear to vary the most, while objective aspects of burden are more similar in nature[13,33,53]. This is mirrored by the finding of low levels of expressed emotions, particularly among Mexican-American and Indian families[6,12]. On the other hand, it has been shown that there is a higher level of stigma and negative conceptualisations of the illness[32,39]. This leads caregivers to try and keep the illness a secret and delay seeking treatment[31,32,34]. Differences have also been identified in the levels of social support available, appraisals of the caregiving situation and coping and help-seeking behaviour. Caucasian caregivers typically employ problem-solving and avoidance strategies more frequently than do African-American caregivers, perhaps because Caucasians perceive caregiving situations as a greater threat or stressor than do African-Americans. Moreover, African-American caregivers are more likely to view their situation in more positive terms, and draw upon religious faith and social networks to mitigate caregiving stress[11,13,21-23,29,52,54-57]. Caregivers from ethnic minority groups appear to have wider and stronger informal support networks than White caregivers[20-23,58,59]. The availability of greater informal support has been linked to the reduced use of formal services and low service utilisation among minority ethnic caregivers[60,61]. Consequently, caregivers from ethnic minorities cope with the stress of caregiving by turning to this readily available means of support from the family and the wider community[10,13,53]. They also seem to use more religious and spiritual methods of coping[57]. Apart from differences in negative outcomes of caregiving, a number of studies have also indicated a higher prevalence of positive aspects of caregiving and greater satisfaction from caregiving among caregivers from ethnic minority groups[10,13,33,35,51,54,61]. However, the reliability of these cultural and ethnic differences in caregiving has often been compromised by methodological shortcomings and inconsistent findings across studies[19,24,51,52,55]. Moreover, socioeconomic status, cultural differences, and within-group variability may confound research findings, making it more difficult to determine how ethnicity or culture differentially impacts the caregiving experience. It has been suggested that cultural or ethnic status may function as a proxy variable for other important factors that are more likely to impact caregiving experiences, such as income, education, health, and family structure[55]. This is not to suggest that ethnic minority status makes families immune to care related stressors. For example, ethnic minority caregivers also report worse physical health and more unhealthy behaviours than whites, after adjustment for socio-demographic differences[13,27]. Nevertheless, there seems to be hardly any doubt that the cultural context shapes the entirety of the caregiving experience and culturally-justified ideologies about roles, responsibilities, and coping shape the caregiving process[20-31]. This has often been referred to as the dimension of "cultural justification"; that is, the process by which caregivers call upon cultural norms and values, styles of communication and coping, and reliance on informal support systems to justify their role and responsibility as primary care providers for their chronically ill family members[26]. Variants of the stress -coping model, which incorporate cultural elements of caregiving have, thus, been proposed to account for these cultural and ethnic differences in caregiving.

FAMILIAL-CULTURAL FACTORS IN CAREGIVING

The list of potential cultural influences on the experience of caregiving is a long one. For sake of convenience, these factors can be divided into those pertaining to family values and norms such as familism, filial obligations or piety, family cohesion and solidarity, and other family values such as reciprocity between adult children and their parents, role modelling of caregiving behaviour for one's own children, and religious and spiritual values emphasising an ethic to care for family members. The second group would include explanatory models of illnesses held by the caregivers and their attitudes towards mental illnesses. The third group would include coping styles, the influence of religion, and the influence of the wider community and social networks. Finally, factors such as acculturation and disadvantaged status could also be important, particularly for ethnic minority groups in the West[21,22,24,28-31].

Familism is a cultural value that refers to the strong identification and solidarity of individuals with their family as well as strong normative feelings of allegiance, dedication, reciprocity, and attachment to their family members, both nuclear and extended[29]. A review of caregivers from six American ethnic groups found highest levels of familism among most ethnic minority groups, compared to White American caregivers[62].

Thus, familism was representative of the individualism-collectivism dimension, and the differences on this measure reflected the effects of acculturation. It was further proposed that higher levels of familism would lead to a more benign appraisal of the stress of caregiving among ethnic minority groups, as it would reflect an underlying desire to provide care for family members[21]. This could explain why caregivers from ethnic minorities report caregiving as less stressful and burdensome. However, the hypothesis that higher levels of familism would result in less burden for caregivers from different cultural and ethnic groups was not borne out by subsequent research. Findings in this regard were mixed, and indicated that familism has a complex relation with caregiving, and the caregiving process may be influenced by numerous other factors[29,63-66]. One reason for such inconsistent results could be that familism is not a unitary construct. In fact, factor analysis has revealed three dimensions of the construct. These include familial obligation, a factor that reflects cultural values that demand caregiving for family members in need; perceived support from the family, a factor that measures cultural expectations that family members will be supportive in times of need; and family as referents, a factor that taps the value that sets up the family as a major source of rules and guidance for how life should be lived. These three dimensions appear to have independent and differing influences on the perception of burden. Accordingly, familism can have positive influences on caregiving distress when the family is perceived as a source of support. However, the dimensions of familism pertaining to a strong adherence to values regarding both feelings of obligation to provide support, as well as behaviours and attitudes that should be followed by different members of a family have been linked to increased caregiver burden and distress[29,63-66].

Filial piety or obligations is a common notion among Asian cultures including the Chinese and Indian people. It includes respect and care for elderly family members, which is explicitly taught to children from an early age. This family-centred cultural construct implies that adult children have a responsibility to sacrifice individual physical, financial, and social interests for the benefit of their parents or family. Filial piety has also been proposed to be a two-dimensional construct: behavioural (making sacrifices, taking responsibility) and emotional (harmony, love, respect). Although some studies have shown that high levels of filial piety make for lowered caregiving burden, this is not a consistent finding. Thus, similar to familism, the obligatory aspect of filial piety norms may constitute a source of stress for some caregivers belonging to ethnic minorities[28,29,31,37,44,67-70].

Another familial factor thought to have a significant impact on the process of caregiving is family cohesion, a process considered important for family functioning. It refers to the emotional bonding that family members have towards one another. Authors have described cohesion to comprise affective qualities of family relationships such as support, affection, and helpfulness[46,52,66,71]. Families with very high levels of cohesion, ("enmeshment") often show communication patterns which are psychologically and emotionally intrusive or inhibitive commonly resulting in poor individuation and psychosocial maturity, whereas low levels of cohesion ("disengagement") can lead to poor affective involvement within the family. Thus, optimal levels of family-cohesion are believed to be ideal for stable family functioning and proper caregiving, and this may differ among ethnic and cultural groups[46,66].

MODELS OF CAREGIVING AMONG DIFFERENT ETHNIC AND CULTURAL GROUPS

Initial attempts to explain differences in caregiving among ethnic minority groups in the West gave rise to the disadvantaged minority group model. This model proposed that because of the historically disadvantaged social history of minority ethnic groups, a number of unique stressors, resources, and vulnerabilities had emerged, which could influence caregiving experiences and caregiver well-being. Caregivers from minority ethnic groups would thus be suffering from the double jeopardy of being from a disadvantaged minority group and being exposed to the negative outcomes, which the caregiving role engenders. In this model, ethnicity was thought to reflect mainly disadvantaged minority status, which was often confounded by socioeconomic status. However, the data did not support this model. Although some studies suggested that differences in caregiving outcomes among minority ethnic groups could be explained by poor socio-economic conditions, the majority of the studies have found lower levels of caregiving burden and stress among ethnic groups such as African-Americans or Hispanics. Moreover, the model overlooked the positive aspects of caregiving, which were more commonly reported by caregivers from minority ethnic groups[29].

Thus, models based on the Lazarus and Folkman's stress-coping approach were proposed instead. Differences in caregiving among diverse cultural groups were explained by a shared common core model, in which caregiving stressors lead to the appraisal of caregiving as burdensome and thus to poor health outcomes (see Figure 1). This model was originally proposed to explain caregiving outcomes in dementia, and was later extended to caregiving experiences with the frail elderly. More recently, this model has provided a framework for examining caregiving in other psychiatric illnesses such as schizophrenia[11,29,31].

The cultural variant of this stress-coping model was first proposed by Aranda *et al*[21]. These authors based their observations on Latino caregivers and concluded that the dimension of individualism *vs* collectivism, or familism, explained the differences in caregiving among different ethnic and cultural groups. They further proposed that cultural influences such as familism operate

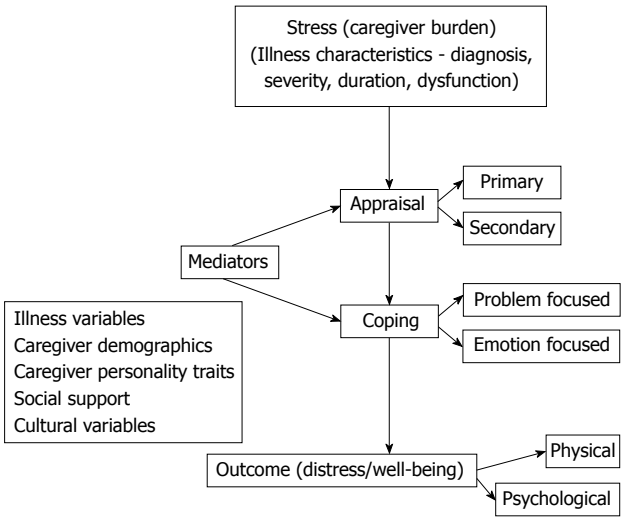

Figure 1 A simplified depiction of the stress-appraisal-coping model of caregiving.

at the level of appraisals of burden. Consequently, higher levels of familism would lead to more benign appraisals of burden, and also to different patterns of using social support, and coping styles, and eventually to lowered perceptions of caregiving as burdensome. Subsequent research on cultural influences in caregiving did not support the predominant role of familism in explaining cultural differences. Other factors such as filial obligations were also felt to be important. Moreover, a single dimension of caregiving from individualism to familism was not found sufficient to explain cultural differences in caregiving. The influence of cultural factors seemed to be more on coping than appraisals of caregiving stress. Therefore, a revised socio-cultural stress-coping model has been proposed[29,31,66]. In this model the impact of cultural influences on caregiving is smaller, more group specific, and varied in direction of effect than anticipated. Moreover, cultural differences appear to operate at the level of coping with caregiving stress and the social support available for the caregiver, rather than appraisals of burden.

METHODOLOGICAL AND CONCEPTUAL ISSUES

The research thus far has clearly demonstrated that there are obvious cultural differences in the experience of caregiving. It has also identified potential cultural factors of interest and proposed models to explain their influence. However, things are far from clear and findings are far from consistent.

One reason for the inconsistent and uncertain nature of the findings could be methodological problems, which affect quite a few of the studies[21,23,24,27,29,55]. Many studies have used purposive or convenience sampling, and the numbers included have often been too small to reach definitive conclusions. Non-caregiving controls have not been used often. Only about half the studies have incorporated conceptual frameworks and models for examining burden and related variables. In certain areas such as caregiver burden, established measures have been mostly used, while in other domains such as social support or coping, there is a great deal of variability and heterogeneity in the measures used[24]. The cross-cultural relevance of the measures used is another problem, which needs to be addressed[23].

In addition, it is becoming increasingly clear that cultural influences are highly complex and multi-dimensional. They are also quite group specific. For example, Dilworth-Anderson *et al*[24] found that White caregivers were significantly more depressed and burdened than African-American caregivers, while Hispanic and White caregivers experienced higher levels of role strain compared to African-Americans. Similarly, Japanese and Mexican-American caregivers reported significantly more psychiatric distress than did White and African-Americans[35,36,64].

Moreover, there appears to be substantial within-group heterogeneity among caregivers, which complicates the accurate attribution of differences among caregivers to specific aspects of their group membership[23]. Cultural values and norms are not static entities; instead they can change from one generation to the next because of the influence of urbanisation, globalisation and acculturation[13,61,72]. The interactions between cultural values and other factors such as gender are also complex. For example, Indian and Chinese studies have shown that effects of filial piety and other traditional values could differ between the genders. Women who adhered to notions of filial piety and Asian cultural values regarding family obligations were more likely to perceive greater burden than men who adhered to the same notions[37,45,68]. Finally, most studies have examined family factors on the dimension of familism (or collectivism) to individualism. Other dimensions of potential importance, such as the difference between shame and guilt cultures, have not received as much attention. There is some evidence to indicate that shame and stigma of mental illness may have more negative effects on Asian caregivers, and prevent them from accessing services[30,34,72,73]. Such evidence indicates the need to examine all possible dimensions, which might explain cultural differences in caregiving.

TASKS AHEAD

Despite the theoretical and methodological problems, the foundations of a culturally based framework of caregiving in chronic psychiatric illnesses appear to have been laid. Research on cultural differences in caregiving has important implications for caregivers and the professionals involved in assisting them. An understanding of the role of culture in caregiving is an essential first step, and it can be hoped that future research will help unravel the complexities of this association. Findings of such research could also be utilised to inform professionals working with culturally diverse groups of caregivers, so that they are more sensitive to the unique needs of these families. Moreover, the results could be used to guide

the efforts to devise culturally adapted versions of interventions to reduce caregiver burden and distress[28-31]. It is for these very reasons that research in this area needs to continue. More pertinently, there is a greater need for research on cultural aspects of caregiving from Asian and other non-Western countries, on lines of the research among ethnic minorities in the West. Finally, other chronic psychiatric illnesses such as schizophrenia and mood disorders also merit examination of cultural aspects of caregiving among them.

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REVIEW

Brain-derived neurotrophic factor as a potential biomarker of cognitive recovery in schizophrenia

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Abstract

Brain-derived neurotrophic factor (BDNF) has been proposed as a biomarker of schizophrenia and, more specifically, as a biomarker of cognitive recovery. Evidence collected in this review indicates that BDNF is relevant in the pathophysiology of schizophrenia and could play a role as a marker of clinical response. BDNF has been shown to play a positive role as a marker in antipsychotic treatment, and it has been demonstrated that typical antipsychotics decrease BDNF levels while atypical antipsychotics maintain or increase serum BDNF levels. Furthermore, BDNF levels have been associated with severe cognitive impairments in patients with schizophrenia. Consequently, BDNF has been proposed as a candidate target of strategies to aid the cognitive recovery process. There is some evidence suggesting that BDNF could be mediating neurobiological processes underlying cognitive recovery. Thus, serum BDNF levels seem to be involved in some synaptic plasticity and neurotransmission processes. Additionally, serum BDNF levels significantly increased in schizophrenia subjects after neuroplasticity-based cognitive training. If positive replications of those findings are published in the future then serum BDNF levels could be definitely postulated as a peripheral biomarker for the effects of intensive cognitive training or any sort of cognitive recovery in schizophrenia. All in all, the current consideration of BDNF as a biomarker of cognitive recovery in schizophrenia is promising but still premature.

Key words: Schizophrenia; Brain-derived neurotrophic factor; Cognition; Biomarkers

Core tip: The lack of diagnostic and treatment markers is one of the most important problems in clinical practice. Brain-derived neurotrophic factor (BDNF) has been proposed as a biomarker of schizophrenia and, more specifically, as a biomarker of cognitive recovery. Evidence collected in this review indicates that there is evidence suggesting that serum BDNF levels are involved in some synaptic plasticity processes. Additionally, serum BDNF levels significantly increased in schizophrenia subjects after neuroplasticity-based cog-

nitive training. All in all, the current consideration of BDNF as a biomarker of cognitive recovery in schizophrenia is promising but still premature.

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INTRODUCTION

The lack of diagnostic and treatment markers is one of the most important problems in clinical practice. Researchers are deeply involved in the identification of validated markers, particularly biomarkers that could be useful in predicting treatment responses to different therapeutics. One of the most important challenges of schizophrenia research is to establish biological markers that can predict clinical outcome and identify clinical stages in these patients. Molecular genetics, analysis of serum and cerebrospinal fluid (CSF), and structural and functional neuroimaging have provided an attractive field of research for biomarkers[1]. For many reasons, such as small effect sizes and individual rarity, gene studies have traditionally shown that genetic markers are not suitable as diagnostic markers[2]. In this line, the study of CSF parameters has yielded a number of interesting candidate biomarkers, but this research has only recent begun[3]. In contrast, despite particularly promising research on neuroimaging, available techniques for evaluating structural and functional brain changes make them unsuitable as biomarkers in schizophrenia[4]. Further biomarker research is needed in schizophrenia. However, evidence suggests both that BDNF is relevant in the pathophysiology of schizophrenia and that BDNF is potentially more useful as a biomarker for diagnostic and prognostic purposes than are other potential biomarkers[5].

A biomarker has been defined by the United States Food and Drug Administration (FDA) as "A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention". Biomarkers have been suggested to have the potential to augment the chances of successful drug and therapeutic development through better target validation, provision of surrogate end-points and patient stratification[6]. Recently, cognitive recovery has been considered among the most important targets in the treatment of patients with schizophrenia. Consequently, the identification of biomarkers of cognitive recovery is relevant not only for diagnostic purposes but also for the development of new approaches to treat cognitive impairment in schizophrenia[7]. Brain-derived neurotrophic factor (BDNF) has been proposed as one of the stronger biomarker candidates in schizophrenia and, more specifically, as a biomarker of cognitive recovery[5].

BRAIN-DERIVED NEUROTROPHIC FACTOR

Neurotrophins are growth factors that play an important role in the survival, development, and functionalism of neurons. They prevent neurons from triggering programmed cell-death, which prolongs their survival. They are also involved in the formation of new neurons in certain areas of the brain. BDNF is one of the most studied neurotrophins. The properties of BDNF vary according to the brain region studied. BDNF has been described as a modulator of neuronal survival and differentiation, synaptic plasticity, and higher order cognitive functions such as learning and memory[8-10]. Moreover, there is also evidence that indicates a role for BDNF in the development of the cardiovascular system[11,12] and in the growth, survival, and chemoresistance of tumour cells in various types of cancer, including Hodgkin lymphoma, myeloma, and neuroblastoma[13-17].

BDNF is mainly synthesised in the brain and spinal cord by glial cells[18], but is also produced by Schwann cells associated with peripheral motor neurons[19]. BDNF is synthesised as a precursor (proBDNF) that is cleaved afterwards to generate the mature protein. Although it was believed that proBDNF had no function, work by Hempstead and collaborators reported that, by interacting with the p75 neurotrophin receptor, proBDNF could induce the opposite effect to that of mature BDNF, leading to cell death[20]. This work has opened a new line in the study of the mechanisms underlying BDNF because mature BDNF mainly acts through a different receptor, the tyrosine kinase receptor B (TrkB)[20]. In addition, it is known that BDNF can pass the blood-brain barrier, reaching non-neuronal tissues, such as the heart, lungs and platelets[21-24]. However, little is known about the function of non-neuronal BDNF. Moreover, BDNF mRNA has been found in several peripheral locations, such as activated human T cells, B cells, monocytes[25], the heart[26], the retina, smooth muscle[12], the lungs[27-28], endothelial cells[29] and platelets[24,29].

Given the difficulty of studying BDNF in situ in the brain, there has been growing interest in the accurate assessment of BDNF activity in the periphery. Studies in murine models have shown a good correlation between BDNF levels in the brain and circulating levels of the protein[30]. The amount of BDNF in serum, plasma and whole blood samples is commonly determined by using ELISA techniques with relatively high specificity and sensitivity. In spite of all the different sources of BDNF, it is believed that BDNF released from platelets is the major contributor to serum samples. BDNF stored in platelets is most likely derived from both the circulating plasma pool and from resident cells in the brain[30] and other organs[22,29,31,32].

Measured BDNF levels are highly dependent on the methodology used[33]. Karege *et al*[34] demonstrated that the stability of BDNF assessed in whole blood, serum, and plasma samples varied among different laboratories. Nonetheless, the accuracy and reproducibility of BDNF determination in serum has been validated[35]. However, there is still little consensus regarding standardised protocols for plasma collection and BDNF dosage. Interestingly, there have been reported changes in serum and blood BDNF levels in patients with neuropsychiatric disorders such as depression[21,36], schizophrenia[37], Alzheimer's disease[38], multiple sclerosis[39], and anorexia[40] when compared to healthy individuals.

GENETIC POLYMORPHISM OF BDNF

The *BDNF* gene (chromosome 11p13-14) encodes a precursor peptide (proBDNF) that is proteolytically cleaved to form the mature BDNF protein. This gene contains a functional polymorphism that has been widely studied in genetic association and gene-environment studies in psychiatry research[41,42]. This single nucleotide polymorphism (SNP) consists of a guanine substitution for an adenine in the position 196 of the gene (rs6265), provoking a change of a Valine (Val) to a Methionine (Met) in amino acid 66 of the protein. As a functional polymorphism, it has been claimed that the Val variant is associated with higher neuronal BDNF secretory activity than is the *Met* allele. Additionally, the co-expression of *Val* and *Met* alleles in heterozygotes results in less efficient intracellular trafficking and processing, leading to decreased BDNF secretion[43,44].

Genetic studies have revealed that the association between BDNF and schizophrenia has not been definitively established. The single nucleotide polymorphisms C270T (in the 5' non-coding region) and Val66Met are two common functional genetic polymorphisms of the *BDNF* gene. A meta-analysis of case-control studies[42] stressed the association of this polymorphism with the risk of schizophrenia and other mental disorders, such as substance-related disorders and eating disorders. This study also showed that individuals with the *Met/Met* homozygous allele had 19% higher risk of developing schizophrenia and other psychotic disorders than did those with the *Val/Met* heterozygous alleles. However, another meta-analytic study of two of the most extensively studied BDNF polymorphisms, *Val66Met* and *C270T*, did not find an association of the *Val66Met* polymorphism with schizophrenia[45]. Nonetheless, several studies have shown positive associations between the BDNF *Val66Met* genetic variant and several aspects of the phenomenology of schizophrenia, such as age of onset, clinical symptoms, aggressive behaviour, suicide attempt, brain morphology, and cognitive function[41].

BDNF LEVELS AND SCHIZOPHRENIA

Schizophrenia has been conceptualised as being essentially a neurodevelopmental disorder[46,47]. It is well known that BDNF plays a key role in a number of processes that are thought to be impaired in schizophrenia, ranging from neuronal differentiation to neurite outgrowth and neuronal survival[48]. In addition, BDNF seems to be crucial to synaptic transmission and various cognitive processes that are severely impaired in schizophrenia. Currently, a considerable amount of data are available that highlight the role of BDNF in the pathophysiology of schizophrenia[49] in both chronic patients and first episodes. Commonly, it has been assumed that determination of BDNF levels in peripheral serum might be a useful measure. On one hand, levels of BDNF in peripheral serum seem to be correlated with BDNF concentrations in the central nervous system[30]. On the other hand, BDNF is able to cross the blood-brain barrier[32]. Unfortunately, the studies that measure serum BDNF concentrations in patients with schizophrenia are not conclusive and have even produced some conflicting results.

The majority of relevant studies report lower serum BDNF levels in schizophrenia patients compared to healthy controls[37,50-54]. However, other studies could not find any differences between schizophrenia patients and healthy controls[55,56]. Further, some studies have even found higher serum BDNF levels in patients with schizophrenia[57,58]. To clarify these controversial results, Green *et al*[59] assessed the published data in a meta-analysis. After a rigorous selection of the works with better methodology, the authors were able to demonstrate reduced serum BDNF levels in schizophrenia patients, not only for medicated patients but also for drug-naïve patients; no differences were shown between males and females. In addition, using meta-regression techniques Green *et al*[59] showed a significant association between reduced BDNF and increased age, but no association was found for medication dosage. In conclusion, after controlling for heterogeneity of samples and methodological aspects, these authors suggested that blood levels of BDNF are actually reduced in medicated and drug-naive patients with schizophrenia.

Although many studies about BDNF levels have been conducted in chronic schizophrenia patients, a few recent studies have examined BDNF profiles in first-episode patients. The earliest study to be conducted with first episodes and drug-naïve patients reported a significant decrease in plasma BDNF levels compared with controls[60]. The authors found a significant association between plasma BDNF levels and positive and negative syndrome scale scores. Since this study, a number of studies have replicated those findings suggesting differences in BDNF levels in first-episode patients. Jindal *et al*[61] showed a significant decrease in serum BDNF levels in patients with first episode schizophrenic psychosis but not in patients with non-schizophrenic psychosis. Unfortunately, they could not find significant correlations between BDNF levels and the severity of positive and negative symptoms or overall functioning. A different study tested

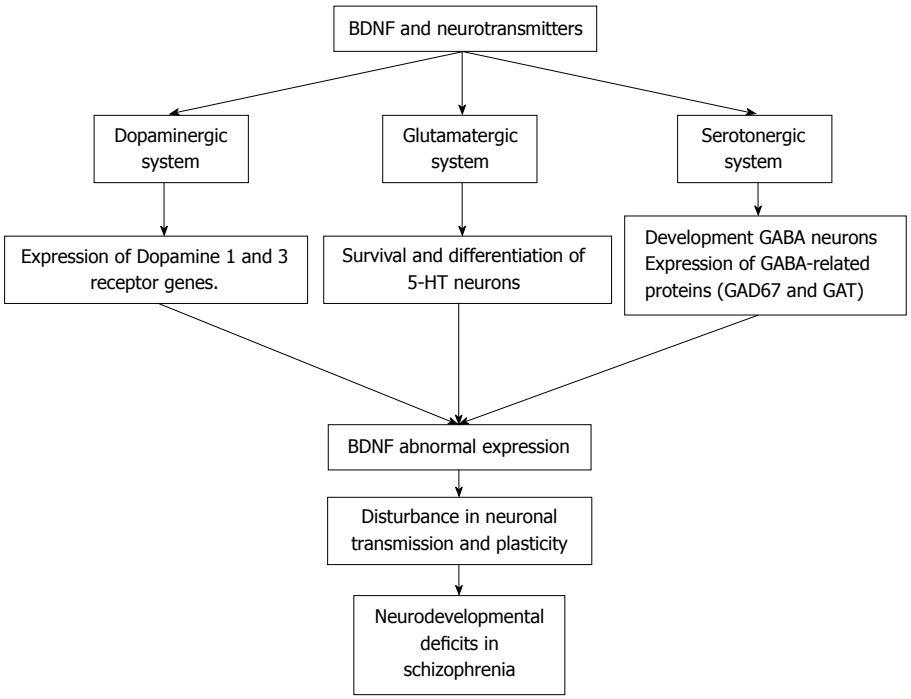

Figure 1 Role of brain-derived neurotrophic factor in synaptic transmission. BDNF: Brain-derived neurotrophic factor.

the presence of cerebrospinal fluid (CSF) BDNF levels in drug-naïve first-episode patients[62]. Compared with controls, a significant decrease in CSF BDNF levels was found and they were significantly related with plasma levels. In addition, CSF and plasma BDNF levels also showed a significant negative correlation with baseline positive symptoms. Finally, a study conducted by the research team of Rizos[63] tried to determine the association between serum BDNF levels and hippocampal volumes in a sample of first psychotic episode drug-naïve schizophrenia patients. The authors found serum BDNF levels significantly reduced in the sample of first-episode patients when compared to levels of healthy subjects. Consequently, hippocampal volume was already decreased at the onset of schizophrenia in first-episode patients. Interestingly, BDNF levels and hippocampal volume reduction were significantly related, which suggests a putative relationship between lower serum BDNF levels and a reduction of hippocampal volume.

BDNF AND NEUROTRANSMITTERS

BDNF plays an important role as a regulator of synaptic transmission and has been associated with the pathophysiology of schizophrenia[64]. Furthermore, its relationship with dysfunctions in the dopaminergic, glutamatergic, and serotonergic neurotransmitter systems has been widely studied.

BDNF is a neurotrophic protein that is synthesised by dopamine cells and has been closely linked to the function of the dopaminergic system. It has been shown to be expressed throughout the cerebral cortex, hippocampus, basal forebrain, striatum, hypothalamus, and cerebellum neurons[65]. With regards to synaptic transmission, BDNF has also been shown to control the expression of D2-like receptors, Dopamine 1 and Dopamine 3 (D1, D3), in adults through the control of specific dopamine genes[66-68]. For this reason, BDNF is an important modulator of the dopaminergic system, and its changes can be observed in the brain and in the plasma of patients with schizophrenia[66].

Exposure to BDNF or a lack of this neurotrophin results in alterations to both excitatory and inhibitory synaptic systems[64]. The role of BDNF in the glutamatergic system has been well studied (Figure 1). BDNF promotes the development of GABA neurons and the expression of GABA-related proteins, such as GAD67 and GAT, in the cortex and other brain regions[65]. In rodents, BDNF regulates the GABAergic system in the hippocampus. In subjects with schizophrenia, altered GABA neurotransmission may contribute to prefrontal cortex dysfunction[69].

Some evidence suggests that BDNF has an influence on the development of the serotonergic system by promoting the survival and differentiation of 5-hydroxytryptamine (5-HT) neurons both *in vivo* and *in vitro*[70,71]. Furthermore, BDNF stimulates the expression of S100 beta in astrocytes and the production of myelin basic protein oligodendrocytes[70]. In mice, alterations in BDNF expression result in physiological disturbances in 5-HT neurons that have been shown to be deteriorated in advanced age[70]. In humans, high levels of central serotonergic activity are associated with high BDNF serum concentrations[72].

BDNF AND SYNAPTIC PLASTICITY

Although the aetiology of schizophrenia is still un-

known, neuroimaging studies have consistently demonstrated brain abnormalities in patients with schizophrenia. These studies revealed significant reductions in gray matter volume in the cortex and hippocampus and decreases in neurons of the dorsal thalamus[73]. Within first-episode psychosis patients, a systematic review and meta-analysis has shown volumetric deficits in the hippocampus and in cortical grey matter, specifically in temporal grey matter[73]. Furthermore, histological studies have shown a significant reduction in synaptic and dendritic markers in the brains of schizophrenia patients[74].

Recent evidence suggests that BDNF has an important role in the growth and development of the central and peripheral nervous system and is associated with disruptions in the brain structure of patients with schizophrenia[75]. In previous studies, BDNF has been reported to regulate axonal and dendritic development and the differentiation and survival of new neurons by increasing the number and length of axons and their branches[64,70]. In mice, BDNF has demonstrated a specific role by promoting survival of embryonic retina ganglion cells and mesencephalic dopaminergic neurons *in vitro*. After administration of high BDNF concentrations in rodents, an extensive neuronal growth was observed[76].

BDNF AND COGNITION

BDNF has been shown to mediate some processes of cognition. It has demonstrated its role as a regulator of axonal and dendritic branching[77,78]. Thus, the process of hippocampal long-term potentiation implies a process of synaptic strengthening associated with learning and memory through its functional TrkB receptor[79,80]. In relation to schizophrenia, a study detected a significant positive correlation between serum BDNF levels and decreased cognitive functioning in 250 Chinese inpatients with schizophrenia[81]. In another study, serum truncated-BDNF abundance predicted a high presence of cognitive impairments, showing 67.5% of sensitivity and 97.5% of specificity[82] in the prediction. This result suggests that deficiency in pro-BDNF processing may be involved in the mechanism underlying the cognitive impairments observed in schizophrenia. In addition, impairment in spatial learning and memory has been found in BDNF-knockout mice[83]. Conversely, single intrahippocampal BDNF administration seems to affect the behavioural flexibility of rats in a Morris water-maze task[84]. Studies have also found impairments in long-term potentiation in BDNF gene-deleted mice[85]. These data support the role of BDNF in cognitive impairments observed in schizophrenia and suggest that BDNF could be a potential marker of cognition, as it is involved in learning and memory processes[5].

BDNF AS A POTENTIAL BIOMARKER

Currently, pharmacological response is mainly a process determined by a trial and error strategy. Identification of biomarkers in the near future could allow us to identify patients who are more likely to respond to a particular treatment and even determine their sensitivity to side effects. However, not only would this allow us to stratify patients according to their likely treatment response but it could also help clinicians and patients to partially avoid the uncertainty of the trial and error process. BDNF has been strongly proposed as a biomarker in schizophrenia and more specifically as a biomarker of cognitive recovery. But, is there now enough evidence to consider DBNF as a biomarker? As previously mentioned, a biomarker needs to have three core characteristics: (1) To be an indicator of normal biological processes; (2) To be an indicator of pathogenic processes; and (3) To be a marker of response to therapeutic interventions.

Indicator of normal biological processes

BDNF seems to play a crucial role in normal cognitive functions such as learning and memory. Its role as a regulator of axonal and dendritic branching has been shown in various studies[77,78]. Thus, the process of hippocampal long-term potentiation, which implies a process of synaptic strengthening associated with learning and memory through its functional TrkB receptor has also been found[79]. In addition to this, BDNF signalling has been implicated in the regulation of adult neurogenesis, suggesting its prominent role in synaptic plasticity and cognition[86]. On the other hand, the genetics of BDNF show that polymorphisms are relevant to understanding normal neurotrophic processes. Variation of BDNF polymorphisms includes a single-nucleotide polymorphism (SNP), rs6265, in the conserved, 5'-pro-protein-coding region; this entails a valine-to-methionine substitution (Val66Met). This last polymorphism has been suggested to cause inefficient BDNF trafficking and a reduced activity-dependent BDNF secretion.

Indicator of pathogenic processes

Some studies have suggested that BDNF is strongly implicated in the pathophysiology of schizophrenia in both first-episode patients and chronic schizophrenia patients. Within first-episode schizophrenia patients, a number of studies have shown a significant decrease in plasma BDNF levels[87]. In addition, serum BDNF levels are lower in chronic schizophrenia patients compared to healthy controls[51]. In relation to reduced brain volumes in first-episode and chronic schizophrenia patients, recent studies have found a correlation to lower serum BDNF levels[63], specifically in reduced hippocampal volume[88]. BDNF levels in serum or CSF have been associated with the presence of schizophrenia in general and to other impairments in cognition. BDNF polymorphism is involved in less efficient intracellular trafficking and processing. This leads to decreased BDNF secretion and possibly to disturbances in neurotransmission processes, which may contribute to prefrontal cortex dysfunction. Neuroimaging studies have shown that reduced brain volumes in first-episode and chronic schizophrenia

patients are related to lower serum BDNF levels[63] and, specifically, to reduced hippocampal volume[88]. Finally, using functional neuroimaging, Eisenberg and collaborators[89] have suggested that Val66Met polymorphism is significantly associated with hippocampal dysfunction.

Marker of response to therapeutic interventions

Studies that aim to measure the effects of antipsychotics on BDNF have produced varying results depending on the type of antipsychotic used in the study[64]. Thus, some studies suggested that typical antipsychotics seem to reduce BDNF expression while atypical antipsychotics could increase BDNF expression, but these studies were carried out as animal experiments. Unfortunately, studies with clinical samples in humans are still scarce[90]. In the particular case of treatments that target cognition, studies are even scarcer. Nonetheless, BDNF has been shown to mediate some processes of cognitive change. There is some evidence about BDNF's role as a regulator of axonal and dendritic branching[77,78]. The process of hippocampal long-term potentiation, which implies a process of synaptic strengthening, has been associated with learning and memory through its functional TrkB receptor[79,80]. Furthermore, a recent study conducted by Vinogradov *et al*[91] has directly tested whether neuroplasticity-based cognitive training is able to modify serum BDNF levels in schizophrenia patients. Samples consisted of 56 schizophrenia outpatients and 16 matched healthy comparison subjects. Both groups were assessed on baseline cognitive performance and serum BDNF levels. Schizophrenia subjects were randomly assigned to either 50 h of computerised auditory training or a computer-game control condition; this was followed by reassessment of cognition and serum BDNF levels. At baseline, schizophrenia participants had significantly lower serum BDNF levels than did healthy controls. Subjects who engaged in computerised cognitive training designed to improve auditory processing showed significant cognitive gains and a significant increase in serum BDNF when compared with subjects who played computer games (control condition). In sum, in a repeated-measures analyses of variance approach, subjects following cognitive training showed a statistically significant gain in global cognition (approximately 0.36 SD) from baseline to endpoint; subjects in the control group showed no change in global cognition (0.01 SD). After 10 wk, subjects following the neurocognitive training were able to increase their mean serum BDNF levels (mean ± SD, 25.27 ± 10.34) to the same level as healthy controls (mean ± SD, 31.30 ± 8.95); the control group showed no change. After the treatment, authors calculated the standardised mean difference (Cohen's d) in BDNF levels between the control group and the therapeutic group and found a medium effect size of 0.67. Although this study has not been replicated, it opens a pathway in clinical research. It is probable that serum BDNF levels would be significantly increased after neuroplasticity-based cognitive training in schizophrenia subjects. If positive replications are published, then serum BDNF levels could be postulated as a peripheral biomarker for the effects of intensive cognitive training or any sort of cognitive recovery in schizophrenia.

Furthermore, pharmacogenetic studies have shown that the BDNF Val66 Met polymorphism could be helpful as an outcome predictor not only for cognitive recovery but also for drug response and adverse side effects. It has been suggested that BDNF polymorphism may be associated with antipsychotic therapeutic effects[41,92,93], treatment resistance[94] and adverse effects including weigh gain[95], tardive dyskinesis[96] and extrapyramidal syndrome[97]. Interestingly, Zhang *et al*[96] have indicated that BDNF genetic variants could be associated with antipsychotic treatment resistance.

CONCLUSION

Evidence collected in this review indicates that BDNF is relevant in the pathophysiology of schizophrenia and could play a role as a marker of clinical response. It has been confirmed that BDNF plays a crucial role as a regulator of synaptic transmission and seems to be related to dysfunctions in principal neurotransmitter systems, such as the dopaminergic, glutamatergic and serotonergic neurotransmitter systems. Particularly, BDNF has been associated with disruptions in brain structure and neurodevelopmental processes. Some studies suggest that BDNF levels are altered in schizophrenia patients. Consequently, the relationship between psychotic symptoms and alterations in the expression of BDNF has been well established. More specifically, BDNF might be playing a role as a marker of antipsychotic treatment because studies show that typical antipsychotics seem to decrease BDNF levels while atypical antipsychotics maintain or increase serum BDNF levels.

Regarding cognitive recovery, the evidence gathered in this review confirms the role of BDNF in brain plasticity and cognition. There is some evidence suggesting the role of BDNF as a regulator of axonal and dendritic branching. BDNF might also be involved in the process of hippocampal long-term potentiation through the process of synaptic strengthening. In patients with schizophrenia, BDNF levels have been related to more severe impairment in cognition. Consequently, BDNF might be proposed as a biomarker of the cognitive recovery process. It has been suggested that BDNF mediates some processes of cognitive change. Thus, serum BDNF levels seem to be significantly increased after neuroplasticity-based cognitive training in schizophrenia subjects. If positive replications are published then serum BDNF levels could be postulated as a peripheral biomarker for the effects of intensive cognitive training or any sort of cognitive recovery in schizophrenia.

Unfortunately, the effect of neuromodulation on BDNF is still far from being completely understood. Moreover, the specificity of BDNF as a biomarker for

schizophrenia cannot be stated because reduction in BDNF has also been observed in patients with neurodegenerative disorders and other neuropsychiatric illnesses. Consequently, more studies are needed in order to establish BDNF as a marker of cognitive recovery in schizophrenia. Cognitive enhancing drugs have not been shown to be completely successful, and consequently, new therapeutic paradigms to improve cognition in schizophrenia need to be tested. The optimal approach may require a combination of specific drug treatment with cognitive training intervention. Finally, examining the prognostic correlation of baseline BDNF levels and the final outcome would be useful in establishing the status of BDNF as a marker of cognitive recovery in schizophrenia. For all these reasons, considering BDNF a biomarker of cognitive recovery in schizophrenia may be promising but still premature.

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CASE REPORT

Dissociative disorder presenting as foreign accent syndrome

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Abstract

The foreign accent syndrome (FAS) is a rare speech disorder, characterised by the appearance of a new accent, different from the speaker's native language and perceived as foreign by others. In the majority of patients, FAS is secondary to focal brain damage caused by stroke or other neurological disorders. Infrequently, FAS has been reported in association with psychiatric disorders, including dissociative or conversion disorders. The case of a young woman with recurrent episodes of speaking with a foreign accent is described. Repeated neurological examinations, imaging and electroencephalography did not reveal any brain abnormality. However, there was a history of a difficult childhood, alcohol dependence in the father, parental discord, alleged sexual abuse in the past, interpersonal difficulties and parental death. Episodes were precipitated by stressful life circumstances and resolved spontaneously, or with supportive treatment. She had additional "suspect" symptoms such as non-epileptic seizures, aphonia and motor paralysis. All these features indicated that a dissociative disorder was involved in the genesis of her FAS. The influence of external factors such as the media was unclear. Generally biological factors have been implicated in the onset of FAS, but the presentation in this young woman suggests that psychological factors such as personality, trauma, stressful life events and psychiatric disorder; familial factors such as parental discord and parental death and family conflicts; and, social factors such the possible influence of the media may also be involved in the production of foreign accents by patients.

Key words: Foreign accent syndrome; Dissociative disorder; Conversion disorder; Psychosocial

Core tip: The foreign accent syndrome (FAS) is a rare speech disorder, characterised by the appearance of a new accent, different from the speaker's native language and perceived as foreign by others. In the majority of patients, FAS is secondary to focal brain damage, but infrequently, it has been reported in association with psychiatric disorders, including dissociative or conversion disorders. The case of a young woman with FAS is described here, which shows that in rare instances dissociative disorder may be implicated in the genesis of the FAS. The aetiology of FAS is complex, and both biological and psychosocial factors could play a role in its onset.

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INTRODUCTION

The foreign accent syndrome (FAS) is a rare speech disorder characterised by the appearance of a new accent, different from the speaker's native language, and perceived as foreign by the speaker and the listener[1-4]. To date, only about 85 patients with FAS have been reported in the literature, beginning with Pick's Czech

patient first identified in 1919[4]. Previous exposure to the new accent is not necessary for the foreign accent to emerge[2]. The syndrome is marked by considerable variability in its presentation, aetiology, and speech characteristics. Clinical manifestations are heterogeneous among patients with FAS, but usually include segmental deficits such as changes in vowel length and tenseness, and prosodic abnormalities such as inappropriate word and sentence stress. It has been suggested that FAS does not reflect any particular language or foreign accent; rather, it is characterised by a generic foreign accent. Though in many instances FAS involves some degree of aphasia or dysarthria, it is usually possible to distinguish the syndrome from the more typical presentations of dysarthrias, aphasias or Apraxia of speech following cerebral damage. Speech abnormalities in FAS can also be differentiated from the dysarthria, mutism, aphonia or stuttering, due to dissociative or conversion disorder. The foreign accent is often persistent, but can also be transient[1-4].

In an overwhelming majority of patients, the syndrome is secondary to acquired focal brain damage. It usually follows stroke, but has been reported in patients with head injury, cerebral haemorrhage, multiple sclerosis and migraine. In most such instances, the lesions described have been found in the dominant hemisphere, and in most cases have involved regions typically associated with Broca's aphasia. Subcortical structures also seem to be consistently affected[1-4]. The foreign accent syndrome has also been reported as a disorder of speech development[5]. The underlying mechanisms of production of the syndrome are still unclear. It has been proposed that a variety of different lesions or factors may be involved in production of the foreign accents by patients[1-4,6-8].

In relatively rare instances, no neurological basis has been found for patients presenting with the FAS, despite repeated clinical examinations and/or imaging studies. Some of these patients have been reported as having a psychogenic cause for their foreign accents[3,6]. In others, the syndrome has been linked with psychiatric disorders such as psychotic or mood disorders[2,7,8]. There are also a few case reports where FAS has been associated with dissociative or conversion disorders[9-12].

CASE REPORT

A 20-year-old, unmarried woman was referred to the department of psychiatry of a multi-speciality hospital in north-India from the neurology outpatient clinic in August 2012. She was accompanied by her 18-year-old brother. Both were orphans and were staying with their maternal relatives some distance away from the hospital. Both the patient and her brother reported that she had had several episodes of speech disturbance since August 2011. During these episodes she would speak almost exclusively in English, which was not her native tongue and in a foreign sounding accent. All these episodes had started suddenly following stressful circumstances. The earlier episodes had resolved spontaneously without treatment in a few weeks to months.

The patient had experienced a very difficult childhood. Her father had a problem of drinking excessively, and becoming violent and argumentative when intoxicated. There were frequent arguments between her parents regarding this issue. Her father died in 2006 of alcoholic liver disease. Following his death, their mother took over the responsibility of running the family farm and looking after the patient and two of her younger siblings. However, there were frequent altercations between her mother and some of her father's relatives who wanted to usurp their land.

In July 2011, the patient changed her school and enrolled in a residential school somewhat far from her home. This was done at her own insistence, because she did not like her old school and the students there. However, she had great difficulty adjusting at her new school. The rules seemed too strict to her and she felt that the students in the new school looked down upon her. So, she was very happy when in about a month's time she was allowed to go home for holidays. The patient remembered being very excited on the bus home and talking endlessly. After reaching home she slept for a while. When she woke up she suddenly started speaking almost exclusively in English with an accent, which was perceived as "foreign" by her family members. She hardly ever spoke in her native languages (Hindi and Punjabi). When forced to do so by relatives she appeared uncomfortable and spoke as if she were a "foreigner". This seemed strange to her family because they hardly ever spoke English at home. After about a week the patient developed several brief (10-15 min) episodes of unresponsiveness, during which she was conscious and aware of her surroundings, but could not talk or move. There were no features suggestive of an epileptic seizure such as loss of consciousness, tonic-clonic movements, incontinence or injury. She was admitted in a local hospital for treatment. The episodes were diagnosed as non-epileptic, and according to the patient she received aversive electric shocks to terminate the episodes. She was discharged after about a week's stay at the hospital. At home for the next two weeks, the patient had great difficulty walking and could not speak at all. She would either crawl, or walk with assistance. Although she tried to speak, it appeared as if "she had lost her voice". She communicated mostly by gestures, and had to be helped by her mother in carrying out all activities of daily living. After two weeks she suddenly regained her ability to walk and talk properly. Following this, she again started to speak mostly in English with a foreign accent. This lasted for about two months, after which the patient gradually switched back to using her native tongue. She was not sent back to the residential school, and stayed back home with her mother and younger brother and sister. She did well till about March 2012, when her mother died rather tragically in a road traffic accident.

The patient who was intensely attached to her mother was grief stricken and missed her mother terribly. However, she appeared to be getting over the bereavement till about four months later, when she again started speaking in English with a foreign accent again. She was brought to the neurology outpatient clinic, where repeated neurological examinations, an electroencephalography (EEG) and a computed tomography scan did not reveal any evidence of cerebral pathology. Hence, she was referred to the psychiatry department to evaluate her for psychogenic causes for her foreign accent.

Apart from her father's alcohol dependence, there was no history of any mental illness in the family. Birth and early development history was unremarkable. She was an average student at school and had no disciplinary problems there. Her younger brother and sister were healthy. Following their mother's death all three siblings were staying with their maternal relatives, and were being well looked after.

On examination she came across as a pleasant mannered and cooperative young woman. She was rather fashionably dressed. Throughout the interview she spoke predominantly in English, with a nasal intonation and an accent vaguely resembling an American one. Her speech also appeared to closely mimic that of anchors and presenters of English language programmes on the television. When forced to speak in her native tongue, she appeared uncomfortable, as if she unfamiliar with these languages. She spoke as an English speaking foreigner would, and seemed to be imitating actors in movies or persons on the television, who spoke with similar accents. Recordings of her speech were not available, but the impression derived from hearing her speak, was that the disturbances were mostly at a phonological level. Segmental and prosodic changes seemed to be involved, leading to changes in patients' accent, and making it sound foreign to her family members. There appeared to be no changes at the semantic and syntactic level from her previous usage of English.

Remarkably, she manifested no distress at her strange way of speaking. She said that she was quite comfortable with her manner of speaking, but her family members found it strange and objectionable. There were no other abnormalities on the mental state examination. Her brother was aware that she had a foreign accent syndrome. He had searched the internet and was concerned that she might have some brain damage. A diagnosis of mixed dissociative disorder according to ICD-10[13] was provisionally made (the equivalent DSM Ⅳ TR[14] diagnosis would be dissociative disorder NOS). Repeated neurological examinations, review of her imaging and EEG findings, and consultation with the neurologists did not suggest a cerebral cause for her symptoms. Although a detailed semi-structured assessment of her problems was carried out, the patient did not cooperate for formal psychological testing. Nevertheless, both the patient and her brother were constantly reassured on the basis of these results that the problem was most likely to be of psychological origin, and there was no evidence of brain damage. The patient was encouraged to discuss her problems and emotional distress in one-to-one sessions with the treating doctor. About four or five such sessions were conducted over the next two months. During these sessions, apart from other interpersonal difficulties, the patient revealed multiple instances of alleged sexual abuse starting from a very young age by different family members and friends. Her speech gradually improved and she lost all traces of her foreign accent during this period. Shortly after this she discontinued therapy on her own accord saying that she feared she might become too dependent on the therapist.

DISCUSSION

The presentation of the FAS in this patient was similar to descriptions of the syndrome, both in instances of it being secondary to dissociative or conversion disorder, as well as those following brain damage[1,2,6-12]. Not only did the patient speak in a language different from her native tongue, but she also used an accent, which was perceived as foreign by her family members. Additionally, when forced to speak in her native tongue she appeared uncomfortable, and spoke in the manner of a foreigner unfamiliar with the language. She had three similar episodes of FAS, all of which resolved within a few weeks to a couple of months. Spontaneous resolution of FAS has also been reported in patients with brain damage and those with psychiatric disorders[2,8-10]. Recurrent episodes have been linked with exacerbations of psychosis in some reports[8].

In this patient repeated neurological examinations, imaging and EEG did not reveal any brain abnormality. On the other hand, there was a history of a difficult childhood, alcohol dependence in the father, parental discord, alleged sexual abuse in the past, family conflict, interpersonal difficulties and parental death. All episodes were precipitated by stressful life circumstances. While in the first two episodes the foreign accent resolved spontaneously, the third episode resolved rapidly with reassurance and supportive sessions. She had additional "suspect" symptoms such as non-epileptic seizures, aphonia and motor paralysis. All these features enabled the diagnosis of a mixed dissociative disorder (ICD 10)[13] to be made with some confidence. The equivalent diagnosis in DSM IV TR[14] would be dissociative disorder NOS.

In DSM-Ⅳ[14], dissociation is defined as "a disruption in the usually integrated functions of consciousness, memory, identity, or perception of environment". As a complex psychopathological process, dissociation occurs on a continuum ranging from minor normative reactions to clinically diagnosable psychiatric conditions. A history of neglect and abuse, or other traumatic events during childhood can be risk factors in the pathogenesis of adult dissociative psychopathology.

In many respects, the presentation of the FAS in this patient was concordant with what has been reported earlier in patients with dissociative/conversion disorder

and FAS. For example, the association with aphonia and the presence of interpersonal conflicts or stressful circumstances, the good prognosis for recovery and spontaneous remission, have all been noted in earlier such instances[9-12].

Other aspects of her presentation were also remarkable. Her younger brother was very much aware of the existence of a foreign accent syndrome and believed it was caused by brain damage. Whether his beliefs influenced the patient's presentation of a foreign accent was not clear. Secondly, the influence of the media on the presentation of FAS in this patient was a distinct possibility. Her accent closely resembled that of television anchors and presenters, as well as movie actors, who frequently speak with similar foreign accents. Indeed, in 2007, there was a much publicised case of a young boy from a remote town in India who suddenly started speaking in fluent English with an American accent[15]. He also claimed to be the reincarnation of a dead American scientist. Though the boy was never formally examined, but certain parts of his presentation suggested the occurrence of FAS. His problems were also believed to be influenced by difficult circumstances, and the electronic media. However, our patient appeared not to have heard of this incident.

FAS usually follows brain damage; hence, biological factors have been implicated in most patients with foreign accents. Purely psychogenic origin of FAS, as in this instance, is a rare occurrence. Moreover, the presentation of FAS in this young woman suggests that psychosocial factors such as personality, interpersonal difficulties, early upbringing, trauma, stressful life events and psychiatric disorder; familial factors such as parental discord and parental death, and family conflicts; and, social factors such as the possible influence of the media and the internet may also be involved in the in the production of foreign accents by patients. Thus, it highlights the fact that in certain patients, psychosocial factors may give rise to a foreign accent, which is virtually indistinguishable from its occurrence following brain damage.

COMMENTS

Case characteristics

The case of a young woman with foreign accent syndrome (FAS) is described here, which shows that in rare instances dissociative disorder may be implicated in the genesis of the FAS.

Clinical diagnosis

The aetiology of FAS is complex, and both biological and psychosocial factors could play a role in its onset.

Experiences and lessons

The presentation of FAS in this young woman suggests that psychosocial factors may also be involved in the in the production of foreign accents by patients.

Peer review

The authors describe a case of young woman with recurrent episodes of speaking with a foreign accent syndrome related dissociative phenomena precipitated by stressful life circumstances and resolved spontaneously, or with supportive treatment. This is very interesting case and well presented.

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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15 Morse SS. Factors in the emergence of infectious diseases.

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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