ORIGINAL ARTICLE

Diagnosis Disclosure of Prodromal Alzheimer Disease-Ethical Analysis of Two Cases

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ABSTRACT: ***Background:*** According to a recent proposal for revised diagnostic criteria for Alzheimer disease, the diagnosis could be made even in the absence of impairment of social function or daily life activities, provided positivity of one or more abnormal biomarkers. The use of the new proposed diagnostic criteria raises ethical issues and needs to be carefully evaluated. ***Method:*** We describe two clinical cases of prodromal Alzheimer's disease and discuss the diagnosis disclosure, taking into consideration several issues: (i) the issue of the boundary between well founded research procedures and clinical practice, (ii) the issue of the fuzziness of the concepts of scientific evidence and scientific uncertainty, (iii) the issue of patient's autonomy and patient's best interest, and (iv) the issue of the patients' specific personal and social context. ***Results:*** The degree of informativeness of the proposed diagnostic criteria for the single patient is already such as to deserve high regard in making the diagnosis and in the diagnosis disclosure process. During the disclosure process, the physician needs to take into account both what is known and what it is not sufficiently known. The patient's personal and environmental conditions should drive the physician to partial or full diagnostic disclosure, or delay communication. ***Conclusion:*** We proposed two different diagnosis disclosure processes, on the basis of the common neurological features and of the different global clinical situations, socio-personal contexts and attitudes towards the communication of the diagnosis.

RÉSUMÉ: Divulgation du diagnostic en phase prémonitoire de la maladie d'Alzheimer - Une analyse éthique de deux observations. ***Contexte :*** Selon une proposition récente concernant une révision des critères diagnostiques de la maladie d'Alzheimer (MA), le diagnostic pourrait être fait même en l'absence d'atteinte de la fonction sociale ou des activités de la vie quotidienne, en autant qu'un biomarqueur anormal ou plus soient positifs. L'utilisation des nouveaux critères à but diagnostique proposés soulève des questions éthiques et doit être évaluée avec soin. ***Méthode :*** Nous décrivons deux observations cliniques de patients en phase prodromale de la MA et nous discutons de la divulgation du diagnostic, en tenant compte de plusieurs aspects : 1) la limite entre des tests de recherche bien établis et la pratique clinique; 2) le flou des concepts de preuve scientifique et d'incertitude scientifique; 3) l'autonomie et le meilleur intérêt du patient; 4) le contexte personnel et social propre à chaque patient. ***Résultats :*** Le niveau informatif des critères diagnostiques proposés pour un patient donné est déjà tel qu'il mérite qu'on en tienne compte lorsqu'on pose le diagnostic et lors de sa divulgation. Pendant le processus de divulgation du diagnostic, le médecin doit tenir compte tant de ce qui est connu que de ce qui n'est pas très bien connu. Le médecin devrait aussi tenir compte de la situation personnelle et contextuelle du patient dans sa décision de procéder à une divulgation partielle ou entière du diagnostic ou d'en retarder la divulgation. ***Conclusion :*** Nous avons proposé deux processus différents de divulgation du diagnostic basés sur les manifestations neurologiques habituelles et sur des situations cliniques différentes, des contextes sociopersonnels différents et des attitudes différentes envers la divulgation du diagnostic.

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We report an ethical discussion on diagnosis disclosure of prodromal Alzheimer's disease (AD) in two clinical cases which deserve high consideration for several reasons. First of all, the two cases raise the issue of the boundary between research and clinical practice, and the issue of scientific uncertainty. Then they stimulate considerations about patient's autonomy and patient's best interest. Finally they show the importance of specific personal and social context when searching for the right action. We will deal with the above general questions not through an exhaustive theoretical discussion, but indirectly through the specific analysis of two cases.

The clinical cases concern two women (AA and BB) referred to the hospital for memory problems, requesting a neurological visit and diagnostic response. At the end of the first clinical

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assessment, the neurologist asked and obtained informed consent for the inclusion in a prospective study on the application and validity of the proposal for revised diagnostic criteria for Alzheimer's disease[1].

The study, favorably reviewed by the local ethics committee, and the scientific methods applied to perform the biomarkers analysis are described elsewhere[2,3]. The two women reported episodic memory impairment and full preservation of daily functions and were positive for all three Alzheimer's biomarkers suggested by the new diagnostic criteria. These two cases were the first found positive to all three biomarkers and therefore the first challenging the neurologist in the diagnosis disclosure process.

The disclosure of the diagnosis of Alzheimer's dementia is difficult and complex even where the diagnosis is based on the widely validated and internationally used criteria. Only very general guidelines for the disclosure of diagnosis are available[4], such that a wide variability in physicians' attitudes and behaviors exist[5], and practices based on local cultural values and preferences prevail. Despite a recent change of attitudes in the medical profession[6,7], in many European countries, including Italy[8,9], the communication of bad news to the patient is usually done so cautiously that often the diagnosis is not really disclosed. The use of the new proposed criteria with diagnostic purposes needs to be carefully evaluated, but, in case, the communication to the patient is even more complicated because the degree of scientific validity of the criteria needs to be taken into consideration. Within this framework, the major ethical question is if and how to communicate the diagnosis to the two women.

Clinical Background

Criteria to date recognized by the scientific community and used in the clinical context for the diagnosis of Alzheimer's disease are those of the National Institute of Neurological Disorders and Stroke - Alzheimer's Disease and Related Disorder (NINCDS-ADRDA)[10] and of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)[11]. On the basis of these criteria a diagnosis of probable Alzheimer disease is made when the patient shows memory and non memory impairment interfering with social function or daily life activities.

Recently a proposal for revised diagnostic criteria for Alzheimer's disease has been developed[1]. According to this proposal, the diagnosis of Alzheimer's disease could be made even in the absence of impairment of social function or daily life activities, provided positivity of one or more abnormal biomarkers among structural neuroimaging with magnetic resonance imaging (MRI), metabolic or molecular neuroimaging with positron emission tomography (PET), and cerebrospinal fluid (CSF) analysis of amyloid beta or tau proteins. The authors of the proposal themselves warn that validation studies are needed to test sensitivity, specificity, and accuracy. Moreover, the criteria are not operationalized, i.e. standard procedures to measure the markers and normality thresholds are not available. So far, the new criteria are used only in research contexts.

With regard to our hospital, all consecutive subjects younger than age 90 who refer to the Translational Outpatient Memory Unit with memory complaints or other cognitive disturbance unaccounted for by focal cerebral, physical, psychiatric, or metabolic diseases are asked to take part in the study on the application and validity of the proposal for revised diagnostic criteria for Alzheimer's disease. The study aims on the one hand to collect data to confirm the validity of the new diagnostic criteria, and on the other hand to give useful diagnostic information to individual patients. Patients with subjective memory complaints or mild cognitive impairment undergo follow up visits every 12 months until the development of dementia. Imaging and biological marker analyses are performed in the imaging and biology laboratories of the IRCCS Fatebenefratelli in Brescia.

Table 1 shows the abnormality of biological markers of AD, as operationalized in the Translational Outpatient Memory Unit. The sources of the normative data used in the study are the following: literature is the normative reference for the neuropsychological findings; for MRI hippocampal volume, a group of 138 healthy subjects between 40 and 87 years of age, 72% females, mean Mini Mental State Exam (MMSE) 28.2, served as norms - these were taken from those enrolled in a study on normal brain structure, as described in detailed elsewhere[14]; for the biochemical analysis of the CSF, controls were 6 healthy persons between 49 and 71 years of age (mean age 61, SD 6.8 y; 20% females; years of education 6.7, SD 2.1 y; MMSE: 28.2, SD 0.9) - normative values have been reported previously[13]. The template used in the application of statistical parametric mapping (SPM) to individual fluorodeoxyglucose (FDG) PET scan is a customized template created from a group of elderly volunteers (Caroli et al. Metabolic compensation in Alzheimer's disease. Poster. American Academy of Neurology 2009 – Seattle).

The Two Cases

In dealing with the two cases, we will first describe the demographic and social aspects, the clinical features and the women's attitude on diagnosis disclosure; then we will propose

Table 1: Abnormality of biological markers of AD, as operationalized in Translational Outpatient Memory Unit

Medial temporal-lobe atrophy on MRI scan	Atrophy score ≥ 2 on left or right hippocampus on visual rating scale of Scheltens et al. [12]. In each hippocampus, atrophy is rated 0 to 1 for normal, 2 for mild, 3 for moderate, and 4 for severe.
Cortical hypometabolism on ^{18}F-FDG PET	Score of 8/36 or higher on visual rating scale assessing metabolism in six bilateral brain areas (frontal, temporal pole, medial temporal, superior parietal, inferior parietal, and posterior cingulate). For each area, glucose metabolism is rated as 0 for normal, 0.5 for uncertain, 1 for mild, 2 for moderate, and 3 for severe [2].
CSF biomarkers	Aß1-42 < 500 pg/mL and total tau >450 pg/mL in 51–70-year-old subjects, and >500 in 71–93-year-old subjects (see Sjögren et al. 2001 [13]).

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our ethical analysis. The two women share the same neurological features, but they have different global clinical situations, different personal and social contexts and different attitudes towards the communication of the diagnosis.

AA

Demographic and social aspects

AA is a 75 years old widow. She has a university degree and worked in the health sector until retirement, 15 years before the assessment. At the time of the assessment (2006), she was living in a small village in North Europe, together with an unmarried son who was only desultorily taking care of her. One of her two daughters was living in a nearby city and the other in another country. The initiative for the neurological visit was taken by one of the daughters, who attended the visit.

Clinical features

AA history was collected from both the patient and her daughter. AA's daughter reported progressive episodic memory problems starting 18 months earlier, confirmed by AA herself. Memory problems had been accompanied by decreased appetite, change of food habits (restriction of food variety), and weight reduction of about 10 kg. She had always enjoyed good physical health and a family history of dementia or Alzheimer's was negative. At the time of the first assessment AA was totally self sufficient in instrumental as well as advanced daily activities: she used to go dancing once a week with her friends and had been able to reach the airport on her own, carry out check-in operations, and take the flight to Italy where she was met by her daughter.

At the first assessment, AA did not complain of somatic symptoms and neurological and physical exams were unremarkable. Her general cognition was normal, instrumental daily functions were preserved, she had full insight of her memory deficits and reported neither depressive nor anxiety symptoms (Table 2). Her performance on learning tests was abnormal on the three objects three places, and below the tenth age- and education-specific percentile on spatial span (Table 3). She achieved normal scores in the other tests.

After the neurological visit, AA underwent MR imaging, FDG PET and CSF exams.

Magnetic resonance (MR) imaging showed mild to moderate aspecific enlargement of frontal, temporal and parietal subarachnoid spaces and moderate dilatation of the lateral ventricles. Medial temporal atrophy on visual rating Scheltens's scale was indicative of mild atrophy (2/4 and 1/4 to the right and left). Remarkably, her normalized hippocampal volume was below the 1st age-specific percentile to the right and left (Figure 1).

Table 2: Demographics and clinical features at baseline of patients AA and BB

		AA	BB
Age, years		75	77
Education, years		18	13
Duration of memory symptoms, years		1.5	1
Global cognition	Mini Mental State Exam	29/30	29/30
Insight	Rating of Awareness Deficits	4/4 (full awareness)	4/4 (full awareness)
	Clinical Insight Rating Scale	0.8 (full insight)	0/8 (full insight)
Disability	Barthel index	100/100	100/100
Mood	Depression (Brief Symptom Inventory)	0.33/4 (absent)	3/4 (severe)
	Anxiety (Brief Symptom Inventory)	0.33/4 (absent)	1.5/4 (moderate to severe)

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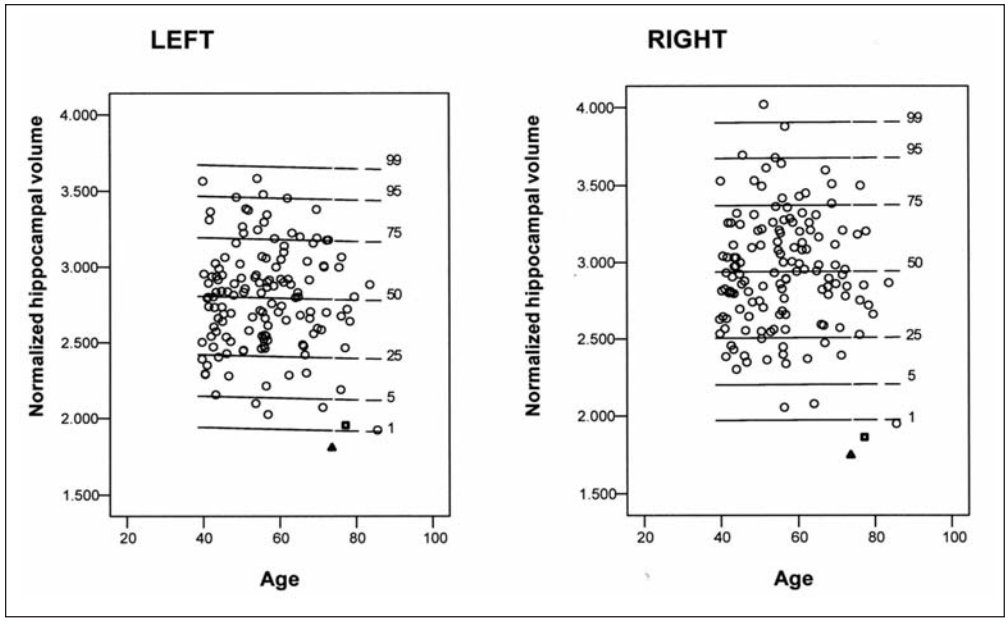

Figure 1: *Medial temporal atrophy of AA and BB. The graphics show that hippocampal volumes of AA and BB were at or below the 1st percentile of the age-specific distribution of cognitively intact older persons (▲AA; ■ BB).*

Visual assessment of FDG PET showed no changes of cortical metabolism. Voxel-based analysis with SPM showed retrosplenial and precuneus hypometabolism (Figure 2).

The CSF biochemical pattern of AA was one of inverted ratio of the abeta42 to tau ratio: abeta42 concentration was 489 pg/ml (normal value (NV) >500 pg/ml) and tau was 607 pg/ml (NV <500 pg/ml) (Figure 3).

Attitude on diagnosis disclosure

The woman did not ask and did not manifest the wish to know anything about the diagnosis during the first assessment nor during the visit for the disclosure of the examinations results. She was collaborative and fully aware of the situation, but she completely relied on her two daughters, who were both present during the visit in which the diagnosis was communicated. The daughters asked to have full disclosure of the diagnosis and prognosis in order to eventually plan the AA's admission to a protected residence near to one of the daughters' house before the mother's loss of capability to adapt herself to a new place.

BB

Demographic and social aspects

BB is a 77 year old, unmarried woman, with a high school diploma, who had been working in marketing until retirement 11

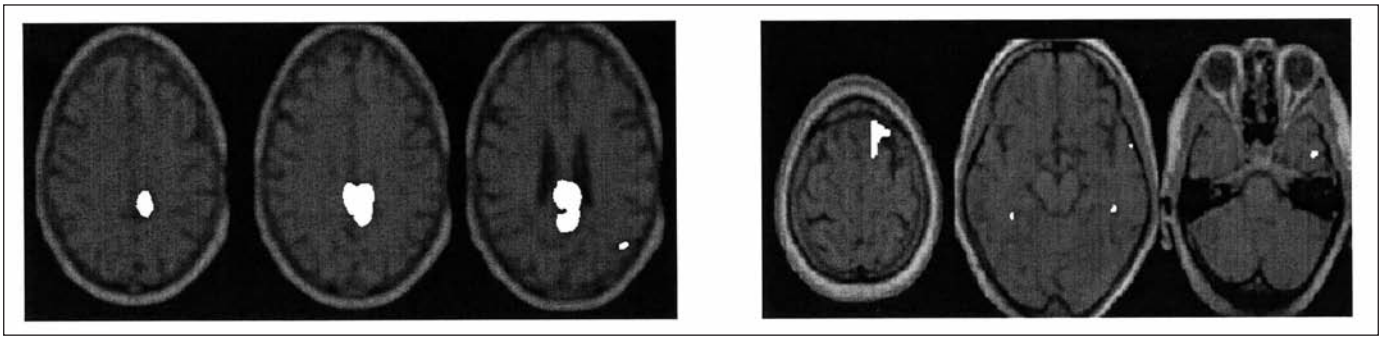

Figure 2: *FDG PET showing retrosplenial and precuneus hypomertabolism in AA (left side) and left frontal and inferior temporal and bilateral enthorinal cortex hypometabolism in BB (right side).*

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years before the assessment. At the first assessment (2006) BB was living alone in a large city in northern Italy, where she had no relatives but friends. Her closest relatives have been living in Argentina for the past few decades.

Clinical features

On first observation, she came unaccompanied and history was collected from her. She reported the recent onset of memory problems. She had always been healthy and had no previous history of psychiatric or neurological diseases. Eighteen months before observation she experienced bereavement and few months before she presented an isolated transient episode of spatial disorientation while in a familiar outdoor place. Worried about these symptoms, she autonomously found out about the Centre for Alzheimer's Disease contacted our Translational Outpatient Memory Unit, and reached our hospital by public transportation.

At the first assessment, BB did not complain of somatic symptoms and neurological and physical exams were unremarkable. Her general cognition was normal, instrumental daily functions were preserved, she had full insight of her memory deficits and reported severe depressive and moderate to severe anxious symptoms (Table 2).

She performed below the fifth age- gender- and education-specific percentile on verbal and non-verbal memory, below the tenth percentile on semantic fluency and visuospatial abilities (Table 3), and within normal limits in the remaining tasks.

After the neurological visit, BB underwent MR imaging, FDG PET and CSF exams.

Magnetic resonance imaging showed mild aspecific enlargement of frontal, temporal, and insular, and moderate of parietal subarachnoid spaces. Enlargement of the lateral ventricles was mild. Medial temporal atrophy on visual rating Scheltens's scale was 1/4 bilaterally (borderline normal). Remarkably, normalized hippocampal volume was at or below the 1st age-specific percentile to the right and left (Figure 1).

Visual assessment of FDG PET showed no changes of cortical hypometabolism. Voxel-based analysis with SPM showed frontal, inferior temporal and enthorinal cortex hypometabolism (Figure 2).

The CSF biochemical pattern of BB was one of inverted ratio of the abeta42 to tau ratio: abeta42 concentration was 230 pg/ml and tau was 549 pg/ml (Figure 3).

Attitude about diagnosis disclosure

The woman was collaborative and fully aware of the situation. On the first visit, her request was sharp and clear: she wanted to know whether she had Alzheimer's disease in order to plan future arrangements for coping with her ensuing disability; in particular she expressed the wish to join her relatives in Argentina before losing her autonomy.

Ethical Analysis

The two women reported episodic memory impairment with full preservation of daily function and asked for a neurological visit and diagnostic response. At the end of the first clinical assessment, the neurologist asked and obtained patients' informed consent for the enrolment in a research protocol within which the Alzheimer's markers suggested by the new diagnostic

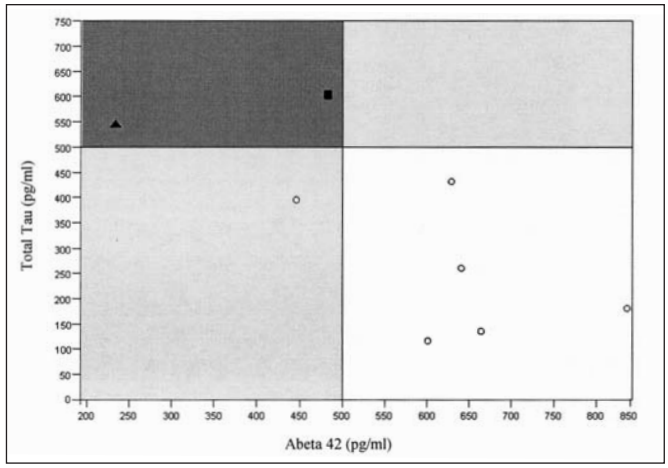

Figure 3: *CSF tau and Abeta42 assays of AA (▲), BB (■), and 6 cognitively intact older persons (○). White denotes the area where both biomarkers are normal, light grey where only one is abnormal, and dark grey where both are abnormal.*

criteria were assessed. During the informed consent process, the study was presented as a not yet fully mature diagnostic path that could nevertheless provide valuable diagnostic information in a proportion of cases. In fact, the team of neurologists involved in the study – even if fully aware of the need of further validation – is strongly convinced that the new diagnostic criteria can in a number of patients be of clinical utility. While consenting to take part in the study, the two women consented in fact both to a new diagnostic path and to the use of the data for scientific purposes. On the basis of a careful, even if not formally structured, evaluation, the two women were considered fully competent to consent.

In the ethical analysis of the two cases, we will first take into consideration the issues related to the common clinical features, pointing out the experimental character of the examinations, the clinical uncertainty of the diagnosis, the lack of effective treatment for the disease and the pre-disability character of the disorder; then we will consider the different personal and social contexts of the two women which could justify different actions. Finally we will present recommendations for the two clinical cases. They are case- specific and related to the situations we are dealing with, but they can represent a suggestion for the solution of other similar cases, after adaptation to different heath systems, if necessary.

Clinical features and related issues

The boundary between research and advanced clinical practice can be fuzzy, especially in the case of disorders whose pathogenesis is still unclear, and for which effective treatments are still not available. The use in a clinical context of research results that have already reached a high degree of reliability can be justified if it is clearly in the patient's best interest. The subject needs to be aware of the experimental character of the diagnostic exams, i.e. the fact that the exams need more

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Table 3: Neuropsychological performance

	AA		BB	
	Raw score	Percentile	Raw score	Percentile
LEARNING				
3 objects 3 places (Prestia 2006[15])	7/9	--	6/9	--
Logical memory (Spinnler 1987[16])	15.5/28	>50th	5.0/28	<5th
Rey figure delayed recall (Caffarra 2002[17])	8/36	10-25th	1/36	<5th
SHORT TERM MEMORY				
Digit span (Wechsler 1997[18])	6	10-25th	5	25-50th
Spatial span (Spinnler 1987[16])	4	5-10th	4	10-25th
LANGUAGE				
Token test (Spinnler 1987[16])	33/36	10-25th	31/36	10-25th
Letter fluency (Novelli 1986[19])	26/3 min	>50th	38/3 min	>50th
Semantic fluency (Novelli 1986[19])	24/3 min	>50th	27/3 min	<10th
VISUO-SPATIAL ABILITIES				
Rey figure copy (Caffarra 2002[17])	28/36	25-50th	28.5/36	<10th

Percentiles are Age-, Gender-, and Education- specific.

validation and are not yet used in clinical context. For these reasons, the informed consent process came before the examinations, deserving time and care to make the patient aware both of the high probable clinical utility and of the experimental character of the new diagnostic criteria. This is a very difficult task to the physician who should give realistic information avoiding at the same time confusion in and misunderstanding with the patient.

With regard to the revised criteria for Alzheimer's disease, previous studies have showed that one positive biomarker can predict with around 80% probability the development of dementia within five years[20-23]. At this moment, there is no empirical basis to believe in a differential accuracy in terms of specificity, sensitivity and predictive power of the three biomarkers[1], and the combined accuracy is yet unknown.

We are facing here a case of "clinical uncertainty" where the diagnostic validity of the three biomarkers is very likely but needs final demonstration in a large representative cohort. This implies that the diagnostic use of biomarkers does not allow to express a definitive diagnosis, but rather a diagnosis with a high degree of confidence, particularly when the three biomarkers are used together. It is in fact likely that specificity increases with each biomarker; differently, the use of the three biomarkers together could decline the sensibility of the diagnosis. Anyway, we regard as a less relevant ethical problem the risk of false negatives than the risk of false positives in the diagnostic process of a disease that has so far no effective treatment. The high degree of confidence of the three biomarkers needs to be taken into consideration in making the diagnosis and planning treatment and monitoring, because this is clearly in the best interest of the subject. At variance, the communication of the diagnosis, that should not ignore the experimental character of the examinations nor the uncertain character of the findings in terms of capacity to predict the development of Alzheimer's dementia, needs to be carefully evaluated. Due to the not yet fully mature diagnostic procedures, the ethical issue here is not only how the diagnosis should be disclosed – as in the case of mature diagnostic procedures – but also whether the diagnosis should be disclosed at all.

Within a good relationship between physician and patient, the possibility to receive or not the examination results needs to be discussed before the exams and subjects should be given the possibility to choose; moreover they should retain the possibility to change their mind at any time and particularly during the visit for the communication of the results. The subjects' understanding of the difference between standard clinical practice and advanced research is very important and needs to be carefully assessed. From an ethical point of view, this kind of discussion and negotiation is mandatory and should always take place.

The availability of disease treatments and the pre-disability character of the disorder play an important role when taking a decision on diagnosis disclosure. At the moment, Alzheimer's disease has no effective treatment. Current drugs – i.e. cholinesterase inhibitors and memantine – can provide symptomatic relief in a number of patients[24], but cannot delay disease progression and, unfortunately, these drugs and cognitive training and rehabilitation, from which there is still no indication of any significant benefits[25], are the only real options today. Due

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to the lack of effective treatments and the theoretical possibility to start the available drugs off-label on the basis of a diagnosis of mild cognitive impairment, a truthful diagnosis disclosure is not necessary to guarantee the subject the best available treatment. The prescription of cholinesterase inhibitors would be based on the physician's belief that the diagnosis is that of Alzheimer's disease, being that these drugs are ineffective in subjects with Mild cognitive impairment[26-28]. Finally, the diagnosis of probable Alzheimer's disease in a very early stage, when the subject has little or no disturbance of judgement and a full preservation of daily life function, raises the question of which disclosure options can better promote the subject's higher quality of life during and after this period. A careful evaluation of what a woman in her late seventies can gain or lose in terms of quality of life after receiving a diagnosis of probable Alzheimer's disease is required.

Socio-personal context and related issues

The two cases are similar with regard to the clinical and biological features of Alzheimer's disease, but they are not from a global clinical point of view, and they deeply differ with regard to their personal and social context. The ethical discussion on the diagnosis disclosure can't ignore the specific personal and social context of the two women, even if the issues raised by that context are not disease specific.

AA has no symptoms of depression and anxiety. She has three children and would not be alone to deal with diagnosis and planning of her future cure and daily life arrangements. She accepted the neurological assessment proposed by her children, was collaborative, and fully aware of the situation. However, she did not explicitly express any interest in knowing her diagnosis and her behavior clearly showed that she relied heavily on her daughters. In this specific case, even if AA is still the main person in the clinical relationship, on the basis of her non-verbal but clearly manifested wishes, the neurologist's primary contacts are in fact AA's children.

BB manifests severe symptoms of depression and moderate to severe symptoms of anxiety. She is living alone and has no relatives in the country where she is living. She would be alone dealing with the diagnosis and the planning of her future cure and daily life arrangements. She herself took the initiative to undergo the first neurological assessment, was cooperative, fully aware of the situation, and explicitly asked the neurologist to know whether she had Alzheimer's in order to plan her future. She is not only the main person in the clinical relationship, but she is also the only neurologist's contact.

Recommendations: searching the best possible solution

Because of the different personal and social context of the two women, the process of the diagnosis disclosure needs to be different, even if Alzheimer's disease marker features are the same.

AA is not living in Italy, so that in the future she will have to refer to other dementia services in her own country. The neurologist has a single visit to explain the examination results and disclose her diagnosis. On the other hand, AA never asked nor showed any wish to be provided any information about her diagnosis and completely relied on her two daughters. AA's behaviour needs to be taken seriously into account and can be rightly interpreted by the physician as a refusal to be informed. For these reasons, the involvement of her daughters alone in the full diagnosis disclosure seems to be at the moment the most appropriate choice.

The diagnosis to be disclosed should be that of Amnesic Mild Cognitive Impairment likely due to Alzheimer's disease. The explanation of this diagnosis needs to underline that the examinations are still experimental and that as far as the scientific community knows, in a high percentage (greater than 80%) of the cases, people who have this kind of clinical picture will develop Alzheimer's dementia within five years. So there is no certainty that a person in this clinical and biological condition will develop Alzheimer's dementia and uncertainty exists on when dementia will eventually manifest itself. The neurologist should suggest that the best thing to do in this case is to start with a treatment which could delay the onset of disability, and to regularly and carefully follow the person, in order to detect cognitive and functional worsening.

Even if AA does not show the wish to know her diagnosis, she is the most important person in the medical relationship. The neurologist needs to speak with her too, with the daughters being present or not according to the women's wishes. The essential elements of the communication should be at least the following two: the clinical situation has to be strictly monitored because the examination results suggest that the cognitive and global functioning could worsen; the prescribed therapy aims to prevent worsening of the clinical condition and deserves compliance. The dementia service that will follow-up AA will be in charge of coming back on the diagnosis communication when the woman eventually manifests her desire to know.

BB explicitly asked to receive full information about her diagnosis in order to plan her future in case of progressive loss of autonomy. She is aware of the situation and fully able to understand. On the other hand she reports severe symptoms of depression and moderate to severe symptoms of anxiety, and she is living alone. The first task of the clinical staff is to understand how much BB can deal with a diagnosis which is both bad and uncertain and how much at the present moment the disclosure could be really useful for her or, on the contrary, could make her condition worse. The best interest of the patient could be different from simply respecting her wish to be immediately and fully informed, and a delay in the full disclosure does not mean that the patient is not respected as an autonomous subject. Delaying full disclosure of what is known and unknown about her mental condition is the good solution until her psychological state improves. The referred diagnosis should be Amnesic Mild Cognitive Impairment (without reference to the probable etiology of the disease). The two essential elements of the communication we have reported in AA's case could be enough for the first step of the diagnosis disclosure.

Delaying the diagnosis disclosure is acceptable in this case because it does not prevent the possibility to prescribe the available therapy; nor the possibility to communicate the full diagnosis at a later date -when BB will be psychologically better and the clinical picture will become clearer; nor the possibility for BB to plan her future before really losing her autonomy.

The neurologist should suggest to BB to involve the general practitioner in the monitoring of her general health and should

schedule the next visit in a short time. In the meantime, the clinical staff of the memory centre need to contact BB periodically by telephone to check her status.

Learning from the follow-up of the two cases

The need to underline what medicine does not know yet (and that could remain unknown) and the call to prudence in the diagnosis communication are confirmed by the follow up of the two cases. One year after the first assessment, the same biolmarkers feature of the two women has exited indeed into two different clinical situations: the disorders of one patient has converted into Alzheimer's dementia; the situation of the other woman has worsened without exiting in Alzheimer's dementia. This does not rule out the possibility of a later conversion, but is a recall of the uncertainty that we are facing.

AA - On 12 months' follow-up, AA's daughter reported marked worsening of attention and episodic memory deficits, accompanied by confabulations, lack of interest in people, and irritability despite the fact that she had been taking donepezil 10 mg for the past ten months. Her daily living activities had also deteriorated: AA was no longer attending her weekly dancing sessions, was cooking sloppily and ate little when alone, while eating hungrily when she found ready-to-consume meals. A few months after the first assessment she had developed theft delusions that were successfully treated with daily haloperidol 0.5-1 mg for two months. On cognitive assessment, she scored 25/30 on the MMSE, failing two items on the spatial orientation, two items on the words recall and pentagon copy. Her performance on all three memory tests had deteriorated significantly, resulting in a performance below the tenth age and education specific percentile. Moreover, Trail making test B-A had worsened from 40 to 168, resulting in a performance below the tenth age and education-specific percentile.

BB - On 12 months' follow-up, BB reported worsening concentration when reading and increased forgetfulness of names of well known people, overlearnt dates, and scheduled appointments and programs, and increased use of her notebook despite the fact that she had been taking donepezil 10 mg for the past six months. She had lost the habit of preparing her meals, preferring to go to the restaurant or buying parboiled ones. She found increasing difficulties in managing her finances and increasing fatigue in daily life activities, even if she reported to be autonomous in all activities. Her sleep quality had also deteriorated. She still maintained her hobbies and interests. On general cognitive assessment she scored 28/30 on the MMSE, failing two word recall items. On neuropsychological testing she showed marked decline in two of the three learning tests (prose recall and Rey figure copy). In particular, the raw score of the former had declined from 5/28 to 2/28 and of the latter from 1/36 to 0/36. The three objects three places test had increased from 6/9 to 9/9. All other tests had remained stable or had minor changes

Conclusion

The revised diagnostic criteria for Alzheimer's disease need to be implemented in research context in order to prove their validity. Nevertheless, the degree of informativeness of these criteria for the single patient is already such as to deserve high regard in making the diagnosis and in the diagnosis disclosure process. In a careful informed consent process, the patient needs to be aware of the experimental character of the diagnostic path and of the meaning of the results and needs to be asked about his/her preference on diagnosis disclosure. During the diagnosis disclosure, the physician needs to take into account both what is known and what it is not sufficiently known. The patient's personal and environmental conditions (psychological status, education, expectations, and social support) should drive the physician to partial or full diagnostic disclosure, or delay communication.

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