

Advances are constantly being made in research on biomarkers, but dementia ought still to be a clinical diagnosis

Biomarkers of dementia

Today about 70 000 people in Norway live with dementia, but this number is expected to double in the course of a few years. As a result, nursing home expenses for care of dementia patients 40 years from now will be twice today's NOK 18 million if we do not find a new and revolutionary treatment (1). However, despite the strong focus on the disorder in the past 20 years, half of dementia patients remain undiagnosed (2). There may be many reasons for this. A lack of objective criteria combined with many doctors' inadequate diagnostic experience are two important reasons. The most common form of dementia is Alzheimer's disease, which affects 60–70 % of dementia patients. Evidence has recently been found that the preclinical phase lasts for many years prior to the debut of symptoms, but does not generate clinical symptoms because the brain's cognitive reserve capacity compensates for accelerating cumulative neuropathological changes (3).

In recent years, substantial resources have been invested in finding and developing objective markers for use in diagnosing dementia diseases, in both the asymptomatic and the symptomatic phase. The focus has been primarily on different types of MRI technology and spinal fluid markers (4), but PET scans of the brain and changes in the blood are also relevant research areas (3). A number of studies have shown that changes take place in the quantity of proteins (dementia markers) beta-amyloid, total tau and phosphorylated tau in spinal fluid in Alzheimer's dementia (4). Beta-amyloid is assumed to indicate the presence of amyloid plaque in the brain, total tau is a marker of neurodegeneration, while phosphorylated tau is probably related to the presence of neurofibrillary tangles. The changes may occur early, partly in the asymptomatic phase. This is reflected in the Dubois criteria of 2007 for Alzheimer's disease, which in contrast to earlier criteria include both MRI changes and changes in spinal fluid markers (5). The criteria are impaired episodic memory function and one of the following: medial temporal lobe atrophy on an MRI scan of the brain, changes in one or more of the spinal fluid markers, typical changes on the PET scan or a genetic mutation (5).

However there has been some doubt as to how useful these criteria are in clinical practice (6). Proposed diagnostic guidelines for Alzheimer type dementia were published recently (7). It is maintained in these recommendations that biomarkers in the spinal fluid can increase diagnostic certainty for persons who meet the clinical criteria. However, the authors do not recommend using biomarkers in routine diagnostics for the following reasons: the clinical criteria result in very high diagnostic precision in most people; more research is required to ensure that the criteria that include the use of biomarkers are properly formulated; there is limited standardization between different laboratories; and access to biomarkers is limited to the first-line service.

We at the Memory Clinic share this scepticism and believe that at present dementia is primarily a clinical diagnosis. We have several examples of patients with evident cognitive impairment with a history of illness and clinical symptoms consistent with Alzheimer-type dementia who are found to have normal spinal fluid markers or normal MRI scan findings. These findings are supported by a Swedish study (6). Our experience is that negative markers do not exclude dementia, but that positive markers support the clinical diagnosis.

Another complex field is differential diagnosis between the various types of dementia. There is some overlapping of the clinical symptoms of different diseases that lead to dementia, and several studies have revealed unexpected neuropathological findings compared with the clinical phenotype. It is therefore interesting to read the article of Skogseth et al. in this number of *The Journal of the Norwegian Medical Association*. It discusses the use of biomarkers in spinal fluid to distinguish Alzheimer type dementia from other types (8). They find relatively high sensitivity and specificity with the aid of spinal fluid markers, but conclude that there is not enough evidence that the markers alone can distinguish one type of dementia from another. The patients in the various studies upon which the article is based were examined in a moderate or advanced stage of the disease, where differential diagnosis appears to be of minor importance.

Today we need first and foremost to be able to distinguish between the various types of dementia in order to evaluate the progression rate and type of medicinal treatment. In addition, patients with some types of dementia show a greater sensitivity to certain drugs. In the future there may be more specific anti-dementia treatment, and it will then be essential to distinguish between the different types.

Dementia is perhaps the most widespread disease of our time, and enormously costly in terms of suffering and money. It is therefore extremely important to continue efforts to develop biomarkers to facilitate diagnosis of clinical dementia, including biomarkers in the asymptomatic phase. As long as we do not have effective forms of preventive treatment, such early diagnosis will of course be of limited use. On the other hand, preclinical diagnosis will exert pressure to find more preventive treatment and knowledge about causal factors. It is therefore very important to increase research efforts in these areas.

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