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Editorial

Imaging biomarkers in multiple Sclerosis: From image analysis to population imaging

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ABSTRACT

The production of imaging data in medicine increases more rapidly than the capacity of computing models to extract information from it. The grand challenges of better understanding the brain, offering better care for neurological disorders, and stimulating new drug design will not be achieved without significant advances in computational neuroscience. The road to success is to develop a new, generic, computational methodology and to confront and validate this methodology on relevant diseases with adapted computational infrastructures. This new concept sustains the need to build new research paradigms to better understand the natural history of the pathology at the early phase; to better aggregate data that will provide the most complete representation of the pathology in order to better correlate imaging with other relevant features such as clinical, biological or genetic data. In this context, one of the major challenges of neuroimaging in clinical neurosciences is to detect quantitative signs of pathological evolution as early as possible to prevent disease progression, evaluate therapeutic protocols or even better understand and model the natural history of a given neurological pathology. Many diseases encompass brain alterations often not visible on conventional MRI sequences, especially in normal appearing brain tissues (NABT). MRI has often a low specificity for differentiating between possible pathological changes which could help in discriminating between the different pathological stages or grades. The objective of medical image analysis procedures is to define new quantitative neuroimaging biomarkers to track the evolution of the pathology at different levels. This paper illustrates this issue in one acute neuro–inflammatory pathology: Multiple Sclerosis (MS). It exhibits the current medical image analysis approaches and explains how this field of research will evolve in the next decade to integrate larger scale of information at the temporal, cellular, structural and morphological levels.

1. Introduction

In medicine, the pace of change in data production is far outstripping the capacity of existing computing models. This increase of data stimulates the need to guide the clinicians within the mass of information to integrate into the medical decision process. This is acutely challenging for brain diseases where the main challenges facing us today include 1) increasing our understanding of central nervous system (CNS), 2) undertaking more effective monitoring of therapeutic procedures, 3) modeling groups of normal and pathological individuals (cohorts) through image descriptors and 4) stimulating new drug design. To address these challenges, current practice is missing computational models able to correlate the large amount of observations produced on patients to underlying pathological phenomena, frameworks to validate these models, and infrastructures to learn these models and apply them to large populations of patients. These issues pose new challenges in the field of medical image analysis, in terms of developing new integrated computational models of living organs and systems capable of mining image descriptors from big databases, assimilating the quantity of imaging data produced about a given patient through compact and relevant mathematical representations, learning dynamics of spatiotemporal data to predict the disease course in individual patients, and reconciling observation and treatment processes (the *theragnostics* concept). Once these major advances will be achieved, the face of clinical practice will change both for professionals (innovations in clinical services, treatment

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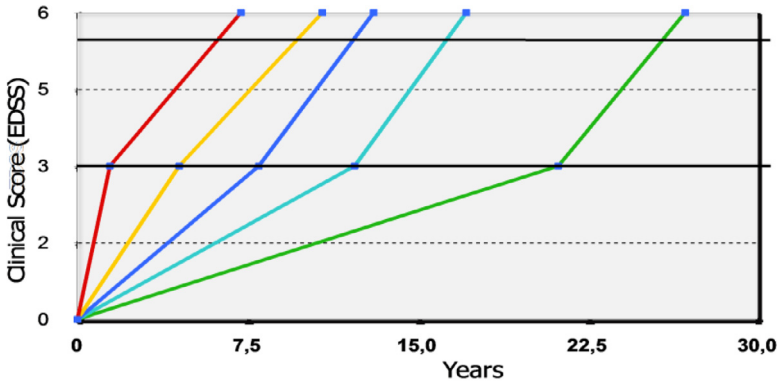

Fig. 1. Epidemiologic study of natural evolution of Multiple Sclerosis disease as a 2-stage course. At onset (time = 0), a new CIS patient may take from 2 (red) to more than 20 (green) years to reach a clinical score highlighting acute handicap (EDSS = 3). Why there is such discrepancy in the population, or why a patient will evolve in the "red" group or in the "green" one is mostly unknown. Having therapy to move a patient from one group (e.g. red) to another (e.g. green) cannot be set up without objective figures to validate this new drug. Imaging is today the only expected instrument to respond to these questions since it is mostly non invasive and can potentially be specific and sensitive (*Study from 2054 MS patients, Univ. Hospital Rennes*). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

delivery, training and education) and for citizens (safer, faster and more accurate medicine).

In this paper, we propose to illustrate the relevance of this evolution of the medical image analysis domain in one acute neuro–inflammatory pathology: multiple sclerosis (MS). We show how computational models have been used in the past to provide some relevant, though limited, markers of the disease and its evolution, but also why these existing computational solutions are limited and how they will evolve in the next decade in order to tackle the remaining challenges and provide imaging biomarkers that become capable of discovering quantitative image descriptors that are not necessarily visible to the human eye and use these descriptors to better represent the dynamics of the pathology and accurately predict the disease course in individual patients.

2. Context: imaging biomarkers in multiple sclerosis

MS is a chronic autoimmune demyelinating disorder of the CNS. It is the principal cause of severe, non-traumatic disability among young adults, affecting more than half a million people in Europe. It has a prevalence rate of 83 per 100,000, and a female: male ratio of nearly 3:1. Onset usually occurs before the age of 30, that is, at a crucial point in an individual's personal, family, professional and social lives. It leads to permanent disability for decades, but has only a marginal effect on life expectancy. MS induces a huge, rapidly increasing, financial burden on society, owing to the approval and more widespread use of new disease-modifying treatments. Disability accumulation in MS is generally acknowledged to be correlated with axonal injury, itself being correlated with the degree of inflammation. However, the interdependence between inflammation and neuro-degeneration, and their respective contributions to clinical deficits remain unclear. Recent epidemiological data from our group suggest that MS is a two-stage neurodegenerative inflammatory disease (see Leray et al., 2010). At each stage, the disease progression follows a different physiopathological pathway: highly variable in the first stage (EDSS < 3), but broadly similar for the whole population in the second stage (EDSS > 3). This new concept highlights the need for a better definition of the early stage, starting with the very first event (clinically isolated syndrome, CIS), and for new research paradigms to better characterize and monitor the progression of the pathology in individual patients. Figs. 1 and 2.

In recent years, conventional magnetic resonance imaging (MRI) has emerged as a powerful noninvasive tool for diagnosis, description of the natural history of the disease and treatment monitoring of MS. In addition, MRI findings have been used to explore drug efficacy in clinical trials.

A number of MR studies show that the principal pathological substrate of permanent disability is axonal loss, detected in MR studies as global atrophy but also as regional atrophy in the white (WM) or grey matter (GM). This atrophy already occurs at early stages of the disease. Axons contribute to about 50% of the WM volume and are, together with neurons, the main contributors of the GM volume. In early progressive MS, GM atrophy seems to be more prominent than WM loss (Dalton et al., 2004; Simon et al., 1999). Longitudinal MR studies in CIS patients have demonstrated that early rather than later focal lesion accumulation is predictive of conversion from CIS to definite MS, accumulation of clinical deficit (Brex et al., 2002; O'Riordan et al., 1998), but also of subsequent brain atrophy. Today, it is not possible to determine exactly when atrophy begins even though it is detectable in CIS cohorts and in early MS patients. Such a knowledge would be important not only for prognostic issues per se, but also crucial to select patients at risk for a severe disease course and to start treatment with disease modifying drugs as early as possible. The need for robust predictive imaging disease markers in MS at presentation is demonstrated by the findings of Brex and colleagues (Brex et al., 2002): after a mean follow-up of about 14 years of CIS patients, about 12% with four or more focal T2-weighted MR lesions did not develop clinically definite MS (CDMS), and thereof only about 40% were only mildly disabled. In the CIS group with one to three focal MR lesions at presentation about one third develops moderate to severe disability after 14 years follow-up. About 90% of CIS patients with one to three MR lesions at presentation develop CDMS 14 years later. Furthermore, using conventional MR methodology in clinical trials of CIS patients, a high proportion of treated patients continue to have MRI activity. MRI measures of inflammation in Relapsing Remitting MS (RRMS) or Secondary Progressive MS (SPMS), such as Gd-enhancement, do not correlate with clinical disability at 1 to 2 years follow-up (Kappos et al., 1999). In conventional MRI studies, Gadolinium enhancement (Gd-DTPA) reflects a severe focal breakdown of the blood-brain barrier (BBB) but this breakdown does not really predict the severity of the pathology evolution.

These different studies show that conventional MRI surrogates provide information at the macroscopic level but lack sensitivity and specificity in identifying the full extent of underlying MS pathology. They also show relatively weak relationships to clinical status such as predictive strength for clinical change (called the