Rachel Clark, CEO of EXCEMED, opened the 2014 Annual Conference on multiple sclerosis (MS) and the scientific organisers, David Bates (Royal Victoria Infirmary, Newcastle upon Tyne, UK), Giancarlo Comi (Institute of Experimental Neurology, Vita-Salute San Raffaele University, Milan, Italy) and Aksel Siva (Istanbul University, Istanbul, Turkey) welcomed around 260 participants to the Conference, which has been accredited for a maximum of 9 hours of European CME credits (ECMEC) and 9.75 CPD credit points by Dubai Health Authority. The local scientific organiser Jihad Inshasi (Rashid Hospital, Dubai Health Authority [DHAI], Dubai, UAE) welcomed the participants to the city of Dubai.

The improvements in both diagnosis and treatment of MS through exciting scientific discoveries in recent decades have changed the medical approach to MS from disease- to patient-orientated, allowing patients to be involved in the decision making process. There is now the opportunity to tailor treatment based on disease activity.

This live educational conference aimed to explore the roles of genetics and environment in the pathogenesis of MS and examine options within the patient-centred approach to clinical management (click here to see the full programme, abstracts and speaker biographies).

**2014 Annual conference**

Multiple sclerosis: improving patient outcomes through scientific and clinical advances

9-10 May 2014 - Dubai, UAE
**Learning objectives**

By attending this live educational conference learners have been able to:

- Describe the latest advances in MS pathogenesis
- Explain the role of genetic susceptibility and environment in MS pathogenesis
- Select the most suitable treatment on the basis of disease phase
- Identify the main predictors of disease evolution
- Summarize how to assess non responders to treatment and how to change therapies

MS is a multifactorial disease - evidence suggests that there is a complex interplay between genes and the environment at work, and that no single factor may be responsible. The disease course varies widely among patients, and the move towards individualised treatment is a positive development in the treatment of this complex and debilitating disease.

The conference programme was divided into three main plenary sessions: **Pathogenesis and basic research**, **Clinical approach to MS**, and **Therapeutic management**. As well as these sessions, the delegates took part in a rotation of **interactive workshops**, and a **round table discussion**.

**Highlights of the meeting**

- The female: male ratio of MS cases is increasing
- Environmental factors may be important in the epidemiology of MS
- MRI is an important tool for MS diagnosis and a key component of MS diagnostic criteria

**Session I: New insights in MS pathogenesis**

**The changing epidemiology of MS**

Presenter: Saeed Bohlega, Department of Neurosciences, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

- MS is increasing in prevalence in some parts of the Middle East. MS is now 2.5 times more frequent in Palestinians than Kuwaitis according to comparative studies of MS prevalence in the region.
- Possible explanations for this phenomenon include the increasing population, thus leading to a higher number of people at risk of developing MS.
- MS prevalence is also lower in regions with widespread helminth infections and poor sanitation.
- Recent studies have shown an increase in the female: male ratio of MS cases ([Figure 1](#)), highlighting the need to focus future studies on lifestyle changes among women, such as smoking, obesity and birth control.

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**Figure 1**: Increase in the female to male ratio

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**Increase in female ratio**

![Increase in female ratio](image)

1 Change in female: male ratio with repeated survey in the same location

A. Alonso, MA Herman, Neurology, 2008

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**Session II: Novel treatments and clinical approaches**

**A new goal for MS treatment has emerged: to reach no evident disease activity (NEDA)**

- Treatment goals are evolving in MS
- Tailoring treatment based on BREMS
- Early treatment can delay relapses, disability, and brain volume loss in the long term
- MS patients are now active players in the decision making process

Be sure to look out for future Excemed events available on the website [here](#).
The role of infections and the environment
Presenter: Orhan Aktas, Department of Neurology, Heinrich-Heine-University, Düsseldorf, Germany

Why does the immune system get activated in MS?
Trying to work out what activates the immune system in MS has long been a burning question for researchers, but the latest research suggests that there is a complex interplay between genes and the environment at work, and that no single factor may be responsible (Figure 2).

Environmental factors may be important in the epidemiology of MS

- Migrants who move from an area where the disease is common to an area where it is rarer show a decrease in rate of disease and vice versa, and risk is largely established during the first two decades of life.
- One hypothesis is that MS occurs after exposure to a common infectious agent, with candidates including Epstein-Barr virus (EBV). The risk of MS is extremely low in individuals with EBV-negative serostatus.
- Vitamin D may also influence MS pathogenesis by modulating the immune system.
- Other non-genetic risk factors that have been identified include smoking and obesity.
- New insights on epigenetic and epistasis have expanded knowledge on the interactions between genes and environment in MS:
  - While the functional role of identified MS risk variants is partially understood, the role of genetic factors in influencing the clinical phenotypes of disease and response to treatment is still unclear.

Deciphering MS pathogenesis: the role of MRI
Presenter: Maria Assunta Rocca, Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

MRI: an important tool for MS diagnosis and a key component of MS diagnostic criteria
- MRI studies have given us new insights into the pathogenesis of MS and factors associated with disease progression
- MRI makes it possible to see dissemination in space (DIS) and time (DIT) and to identify the neuroradiological red flags typical of other conditions that may resemble MS in the clinic.
- Advanced MRI techniques can now identify lesions in brain regions not previously thought to be involved in the MS pathogenic process, such as normal appearing white and grey matter and cortical areas, adding more insights into MS pathogenesis (Figure 3).
  - Leukocortical (type I) and subpial (III-IV) cortical lesions are potential cortical biomarkers of cognitive and neurologic disability.

Genetics of MS
Presenter: Filippo Martinelli Boneschi, Neurological Complex Disorders, Department of Neuro-rehabilitation, INSPE Scientific Institute San Raffaele, Milan, Italy

Genes involved in the pathogenesis of MS were first identified in 2007 from genome-wide association studies (GWAS). Since then, research has gathered pace; as well as the genes related to immune system pathways which are known to drive MS more than a hundred risk variants for MS have been identified outside the HLA region, and other low frequency and rare variants are expected to be discovered in the future. There are now 110 established multiple sclerosis risk variants outside the HLA region, but there are other low frequency and rare variants to discover.

- Non genetic risk factors for MS include vitamin D levels, smoking, obesity and EBV infection.
- There are other mechanisms which could explain the influence of genetics on susceptibility to the disease (epigenetics, interaction between genetic and non-genetic factors).
- The functional role of identified MS risk variants is only partially understood.
- The role of genetic factors in influencing the clinical phenotypes of disease and response to treatment is still unclear.

Results from this approach contribute to firmly establish that genes and pathways involved in the immune response are the major drivers of MS risk

Leena Peltonen
The role of neurophysiology

Presenter: Letizia Leocani, Institute of Experimental Neurology, University Vita-Salute IRCCS, San Raffaele Hospital, Milan, Italy

- MS-related damage is caused by segmental demyelination and axonal degeneration:
  - This can be measured and monitored by conduction velocity and amplitude, respectively.
  - Delayed latency is most often detectable in asymptomatic patients and predicts future axonal loss.
  - Reduced amplitude is a sign of clinical impairment and becomes permanent when axonal loss occurs.
- Studies on optimising the use of neurophysiological techniques, particularly evoked potentials (EPs), show promise for identification of patients who are more likely to develop future disability and who need intensive monitoring and treatment.
  - Visual evoked potentials (VEPs) are usually absent in neuromyelitis optica (NMO)
  - VEPs are less sensitive as an indicator in clinical isolated syndrome (CIS), but subclinical motor evoked potential (MEP) abnormalities may positively predict future motor function involvement.
  - In fact, data suggest that MEPs may predict disability at 2 years in relapsing-remitting MS (RRMS) with 80% accuracy.
  - Optic coherence tomography (OCT) has also emerged as a reliable tool for diagnosis and monitoring of axonal loss after an episode of optic neuritis (Figure 4).

Table 1: Comparing clinical utility of EPs in MS

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>SCARCE</th>
<th>GOOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of clinically silent lesions (anywhere in CNS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indication on underlying pathology (demyelination, axonal damage/block)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>MONITORING (e.g. assessing treatment efficacy)</th>
<th>SCARCE</th>
<th>GOOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease activity (lesions anywhere in CNS)</td>
<td></td>
<td></td>
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<tr>
<td>Relapse confirmation (vague symptoms)</td>
<td></td>
<td></td>
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<tr>
<td>Disease progression (clinically relevant pathways)</td>
<td></td>
<td></td>
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<tr>
<td>Functional improvement (clinically relevant pathways)</td>
<td></td>
<td></td>
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<tr>
<td>Prediction of future disability progression (?)</td>
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</table>

Session II: Clinical approaches to MS

MS management is now comprised of disease modification, maintaining and improving physical cognitive function, and quality of life.

In the near future we should be able to produce risk forecasts on individual patient level, incorporating not only further clinical aspects of the disease (e.g. cognitive impairment), but also genetic, immunological, neurophysiological and radiological findings.

Evolving Treatment Goals
Treatment goals are evolving in MS

Trying The course of MS has changed since the advent of disease-modifying agents. These new drugs provide many benefits for patients, including fewer and less severe relapses, better recovery after relapses, prevented or postponed progression of disability, reduced accumulation of disease burden or decreased brain lesion activity, and improved quality of life, cognitive functioning or less fatigue. This has led to evolving treatment goals, with the well-being of the patient now an important consideration in the therapeutic contract.

Prognosis from natural history
Presenter: Roberto Bergamaschi, National Neurological Institute C. Mondino, Pavia, Italy

Tailoring treatment based on BREMS
- There are several clinical factors that may help define MS prognosis from natural history, particularly male gender, and an older age of onset of the relapsing-remitting phase of the disease.
- The Bayesian Risk Estimate for Multiple Sclerosis (BREMS) was discussed as an important tool for predicting secondary progression and to predict poor outcomes at an early stage, particularly when assessing and comparing the effects of disease-modifying drugs.
- BREMS is based on clinical factors including gender, pure motor onset, sphincter involvement and number of motor relapses. The BREMS might help tailor treatments for individuals based on the presence or absence of negative prognostic factors.

Defining Breakthrough Disease Activity: Targeting Disease-Free Status
Presenter: Robert J. Fox, Mellen Center for MS, Cleveland Clinic, Cleveland, USA

In the last few years, a new goal for MS treatment has emerged: to reach no evident disease activity (NEDA)
- NEDA was first reported as a concept in 2009, and since then a plethora of clinical trials have demonstrated the effectiveness of disease-modifying drugs according to this endpoint, which includes measures of:
  - Number of clinical relapses
  - MRI activity
  - Disability progression.

How approaches to MS treatment have changed over the years:
- Pre-1990s: “There’s nothing we can do”
- 1990s: There are treatments that will help some
- 2000s: If one treatment doesn’t seem to work, then change to a different one
- 2014: We’re aiming for no evident disease activity

Treating to target requires individualised planning of treatments and assessment for each patient, taking into account severity, recovery from relapses and lesion characteristics:
- Unresolved issues in individualising treatment include optimal definition of NEDA and breakthrough disease, incomplete assessment, and integration of NEDA with treatment risks.

Evolving Paradigm: Individualized Treatment Based on Projected Disease Course

Gd-gadolinium, NAbs=neutralizing antibodies

10
Predictivity of treatment response
Presenter: Mar Tintorè, Multiple Sclerosis Centre of Catalonia (Cemcat), Neurology-Neuromimmunology Department, Vall d’Hebron University Hospital, Barcelona, Spain

Predictors of response to treatment are necessary to optimise patient management
- Response to treatment is highly heterogeneous among MS patients and therefore predictors of response to treatment are needed to optimise patient management.
- Can we identify subgroups of patients who show different treatment effects? Clinical, MRI and biological parameters can all define the predictivity of response to treatment.
  - A later age at onset, a lower disability and a lower number of GAD lesions at baseline MRI were predictors of treatment efficacy, BUT it is not clear whether these parameters are really predictors of treatment response or prognostic factors.
  - Overall, clinical parameters show a low sensitivity in defining the prognosis.
  - The risk of disability is greater in patients with increased MRI activity.
  - Brain atrophy measurement is not always a reliable measure, due to technical difficulties and bias during the acquisition and data analysis phases.
- Clinical evaluation and MRI studies together could be more useful in defining the prognosis (Figure 6).

How to keep patients on treatment
Presenter: Carlo Pozzilli, Department of Neurology and Psychiatry, “La Sapienza” University of Rome, Rome, Italy

Non-adherence to therapy is an important issue in the field of MS
- Patients don’t always take their medication because treatment regimens may be complex, side effects can be intolerable, or patients fail to understand the need for the medication.
- One in three MS patients discontinues interferon beta (IFNB) treatment within 3–5 years, with 10–20% discontinuing within the first 3–6 months.
- In comparison, drop-out rates in clinical trials are less frequent (8–14%; 2–3-year data)
- Early treatment is important to reduce inflammation and prevent disability and disease progression.
- To be effective, a treatment should be administered in the right way and at the right dosage.
- It is important to share decisions about treatment with patients and relatives.
- Symptoms should be managed as soon as they are identified because they may negatively impact on adherence to treatment.

Successful long-term management of MS
- Patient selection for therapy: disease stage and course timing
- Patient education: realistic expectations (must believe that therapies can make a difference)
- Reinforcing goals: perception of neurologist as supportive of therapy
- Managing and explaining side effects
- Support through therapy initiation
- Available specialised support and advice

Workshops
Throughout the meeting, six interactive workshop sessions were available in rotation, so that participants were able to attend all of them, with the chance to share opinions and understanding of these different MS related topics:

Treatment initiation and therapeutic contract
Led by: Carlo Pozzilli, Department of Neurology and Psychiatry, “La Sapienza” University of Rome, Rome, Italy and Aksel Siva, Department of Neurology, Istanbul University, Istanbul, Turkey

Management of MS has been significantly improved by more recently developed second-line treatments, which include monoclonal antibodies and new oral agents, which show greater efficacy and

Figure 6: A monitoring algorithm for assessment of clinical response

* Substantial new T2 activity is defined as >4–5 new T2 lesions in 1 year of treatment, or >1–2 new T2 lesions if the reference MRI scan to assess new T2 lesion formation is obtained at least 6 months after initiating therapy.
probably better patient compliance compared with the injectables, but which may also carry novel safety and tolerability concerns. New drugs for MS need to be placed within this evolving marketplace, where ease of delivery together with efficacy and side effects needs to be balanced against the known issues but also the known long-term safety of standard injectables.

How to manage response to first-line therapies
Led by: Orhan Aktas, Department of Neurology, Heinrich-Heine-University, Düsseldorf, Germany
and Gilles Edan, Centre Hospitalier, Universitaire de Rennes, Rennes, France
The workshop looked at aspects of first-line therapy for MS, including indications for switching from one therapy to another. The investigation of response to treatment should be carefully investigated and non-responders clearly defined. Both clinical evaluation and MRI studies should help neurologists make the right decision. Adherence to treatment may profoundly influence the response to treatment and should be assessed during the patient follow-up.

Therapeutic options
Led by: Giancarlo Comi, Department of Neurology, Institute of Experimental Neurology, Vita-Salute San Raffaele University, Milan, Italy
and Peter Rieckmann, Bamberg Hospital and University of Erlangen, Bamberg, Germany
The experts looked at disease-modifying drugs old and new, illustrated with four clinical case vignettes to define scenarios in which therapeutic options are key questions at patient’s consultation, including Initial diagnosis, Discomfort with injections, Planned pregnancy, and Breakthrough disease.

Role of MRI in monitoring treatment
Led by: Nicola De Stefano, Neurology and Neurometabolic Unit, Department of Neurological and Behavioral Sciences, University of Siena, Siena, Italy
and Maria Assunta Rocca, Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy
The workshop looked at how MRI techniques have provided useful markers to monitor treatment effect in MS clinical trials. Evaluation of potential new therapies for MS has been facilitated by the use of standardised MRI protocols in phase II and III trials, and the combination of clinical measures of disease activity with imaging evidence of formation of new lesions seen with MRI may have a role in identifying non-responders to first-line treatments. The routine use of MRI is therefore recommended to monitor disease activity during treatment, both to facilitate early identification of those patients who could possibly benefit from a different therapeutic approach, and to identify signs of side effects. It is likely that in the near future, novel MR metrics to assess treatment response in clinical trials and in daily-life practice will be proposed, validated and used.

Genes and environment
Led by: Gilles Edan, Centre Hospitalier, Universitaire de Rennes, Rennes, France
and Filippo Martinelli Boneschi, S Centre, Division of Neuroscience, Institute of Experimental Neurology (INSPE), Scientific Institute San Raffaele, Milan, Italy
The workshop reviewed the main findings on genetic susceptibility and the role of environmental factors in disease onset and progression. Evidence was presented that, while MS is a multifactorial disease involving both genetic and environmental factors, genetic factors outweigh environmental factors in disease pathogenesis. The groups looked at challenging areas likely to occur in the near future, including interpretation of genome-wide association studies and the contribution of genetics to clinical practice.

Patient engagement in the decision-making process
Led by: Dawn Langdon, Department of Psychology, Royal Holloway University of London, London, UK
and Alessandra Solari, Unit of Neuroepidemiology, Foundation IRCCS, Neurological Institute C. Besta, Milan, Italy
Dawn Langdon and Alessandra Solari explored the role of the patient in MS management today, emphasising the importance of nurturing the relationship between the patient and healthcare professionals (HCPs) for optimal management and outcomes. It is now recognised that patient engagement, and their involvement in decision making, is a key aspect of this partnership. MS poses certain challenges to engagement, with cognition, depression, fatigue and other symptoms requiring skilful communication and understanding by HCPs to maintain and support their engagement in decision making.

Roundtable discussion session

Patients’ perception and patient reported outcomes (PROs)
Introduced by Bassem Yamout, Multiple Sclerosis Center, Clinical Research, American University of Beirut Medical Center, Beirut, Lebanon
Chairs: D. Bates (UK) and B. Yamout (Lebanon)
MS patients are now active players in the decision-making process: After the presentation by Bassem Yamout, key opinion leaders discussed emerging aspects in the management of MS during the roundtable:
- Patients are having ever greater input into the decision making process surrounding their disease management. Their perception about the disease and the treatment response is a key component of MS management. However, patients often don’t understand the relevance of avoiding one relapse every 4 years, and doctors and patients don’t always agree on what is important about their disease. Patients’ quality of life (QoL) is much more important to them than clinicians have realised.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Clinicians</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental health</td>
<td>25/7</td>
<td></td>
</tr>
<tr>
<td>Physical function</td>
<td>22/20</td>
<td></td>
</tr>
<tr>
<td>Physical role limitation</td>
<td>17/21</td>
<td></td>
</tr>
<tr>
<td>Emotional role limitation</td>
<td>16/2</td>
<td></td>
</tr>
<tr>
<td>General health</td>
<td>14/4</td>
<td></td>
</tr>
<tr>
<td>Social function</td>
<td>14/13</td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>13/3</td>
<td></td>
</tr>
<tr>
<td>Bodily pain</td>
<td>5/4</td>
<td></td>
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</tbody>
</table>

This cross-sectional study demonstrates that patients with MS are less concerned than their clinicians about physical disability in their illness and more concerned about their quality of life.

Significant predictors of quality of life in patients with MS include depression, social support, religious beliefs, education and standard of living.
• Patient education can reduce disease progression: The relapse rate was lower by 0.8 in educated patients through 2 years of monitoring.

![Relapse rate comparison](image)

- Traditionally, outcome scales based on the clinical perspective have been applied both in clinical practice and in the scientific setting, but current outcome measurements do not allow the full benefit of new drugs to be assessed.
- In order to make the role of patients more relevant, innovative, patient-centered outcome measures that go beyond relapse reduction and EDSS stabilization have been developed. The “MS in the 21st Century” initiative defines how multiple sclerosis (MS) treatment and standards of care should look today.
- The panel of experts concluded that new endpoints in clinical trials should include patient-reported measures as well as functional assessments and biomarkers. Incorporating PROs in patient management will likely increase patient engagement and adherence to treatment.
- Debate continues on which PROs should be chosen for individual patients, and how this new approach can be translated into routine clinical practice.
- The need to include these measures as key endpoints in future clinical trials was also highlighted during the roundtable discussions.
- However, it was agreed that incorporating patient-reported outcome measures in patient follow-up is likely to increase patient engagement and adherence to treatment. Shared decision making between patients with MS and their doctors is evolving.

**Session III: Therapeutic management**

**The dilemma:**
- giving “a long term treatment” to an individual who doesn’t require it, or to whom such a treatment may worsen the disease, is causing harm!
- withholding “a beneficial treatment” from an individual who requires it, or to whom such a treatment may improve the disease’s outcome, is also causing harm!

This year, the thorny issue of when to initiate treatment was discussed in a workshop and also the topic of a lively debate. Giancarlo Comi (Vita-Salute San Raffaele University, Milan, Italy) urged those treating MS patients to start treating immediately, while Aksel Siva (Istanbul University, Istanbul, Turkey) made a compelling case to “wait and see”.

**Early treatment can delay relapses, disability, and brain volume loss in the long term**

The case for early treatment is based on there being a “window of opportunity” to prevent irreversible axonal damage. Early treatment will prevent the irreversible damage to the nervous system which occurs very early and is at least partially related to inflammation in MS. It is also well known that the early course of the disease influences long-term outcomes. Immunomodulatory treatments can reduce the inflammation that predominates in the early phases of the disease, and patients with greater clinical activity during their first year of treatment were at increased risk of continuing with relapses and/or sustained disability in the next 2 years. Data from several clinical trials show that treatments for MS are more effective in the relapsing remitting phase than in progressive phase of disease.

**But... Not all patients with RIS or CIS will develop MS**

The arguments to wait before treating focused on the fact that not all patients are biologically equal and will vary in their responses and outcomes. Therefore there is a case to be more selective before making “life-time” treatment decisions.

While neuroradiological examinations are now detecting increased numbers of patients with radiologically isolated syndrome (RIS), many will not go on to develop MS. Is RIS the earliest stage of MS and should individuals with RIS be considered for early treatment as well? Similarly, not all patients with clinically-isolated syndromes (CIS) go on to develop MS and not all untreated CIS patients develop MS or MS-related disability. These studies provide evidence that a “benign MS” exists, and supports the strategy of wait and see, particularly in patients thought to be at lower risk of developing MS.

**Assessing treatment failure**

**The dilemma:**
...if an area of the CNS is lesioned, another area can take over its functions...

There is adaptive reorganisation!

Also debating were Nicola De Stefano (Neurology and Neurometabolic Unit, Department of Neurological and Behavioral Sciences, University of Siena, Siena, Italy) and Vittorio Martinelli (Neurology Unit, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy), who explored MRI versus clinical sciences to assess treatment failure.

Nicola De Stefano highlighted the importance of MRI assessment of lesions and brain atrophy to predict prognosis, as well as its key role in the recently-developed Rio score to predict response to treatment. Even when clinical signs are absent, MRI can detect brain damage.
References


