Brain MRI in Mitochondrial Disorders

Valorisation

Mitochondrial disorders, considered as the most common inborn error of metabolism in children and most prevalent group of inherited neurological disorders in adults, often cause multisystem dysfunction leading to a characteristically complex clinical picture with significant morbidity and mortality.[1,2] While the inherent heterogeneity and complexity associated with these disorders pose diagnostic and management challenges to the physicians involved in the care of patients, the diagnosis or suspected diagnosis of a mitochondrial disorder, pose considerable challenges to the families as well.[3] Firstly, the diagnostic evaluation in patients with suspected mitochondrial disorders is "time-consuming, logistically demanding, cost-intensive, and often associated with inconclusive or negative results, and above all, it is frequently not initiated at all, why many of these patients go undetected for years or forever".[4] Secondly, even though there has been tremendous advancement in understanding the genetic basis of mitochondrial disorders in recent years, the information on the course and prognosis still remain the biggest challenge in patient management. Thirdly in view of the propensity to affect the central nervous system, chronic disability is the rule which cause considerable economic burden to families as well as to the health care system.[3] Taking all these factors together, the individual disease burden is extensive, resulting in substantial direct and indirect health care costs to the patient and society as a whole.[1]

The studies in this thesis are relevant to address the above-mentioned issues faced by the families of patients with mitochondrial disorders. Our data (chapter 2-5) demonstrates that Brain MRI is an invaluable tool in guiding diagnosis, prognosis and therapy in mitochondrial disorders. This is important for clinical practice of adult and paediatric neurologists, geneticists, radiologists and for patients, patient organizations and advocacy groups themselves. Our results have substantial implications for evaluation, assessment of intervention outcomes and may guide evidence based management guidelines.

Shortening the diagnostic odyssey thereby reducing the cost of diagnostic process

The work described in this thesis examined three important aspects of mitochondrial disorders, the clinical phenotype, genetic basis and most importantly the Brain MRI findings. We first critically analyzed the brain MRI findings of mitochondrial disorders reported in literature. We then proceeded to characterize the MRI findings in specific genotypes in a relatively large cohort of patients to establish correlations between specific genotypes and MRI phenotypes. This study provides valuable data on the MRI phenotypes in a rare group of disorders (chapter 2). Mitochondrial disorders are rare and not many physicians are familiar with the clinical and MRI findings to suspect the diagnosis at an early stage. MRI is one of the earliest and easily

available tools available to the clinician and knowledge of the various MRI findings and their correlation with the phenotype and genotype is of paramount importance in the diagnostic evaluation of patients and for optimal patient care. MRI helps the physician to suspect the diagnosis early in the clinical course and target the investigations in specific directions thereby reducing the cost and length of investigations. In other words, for the clinician, it gives a cost effective way of analyzing the problem, nature and extent of the CNS involvement and provides an easy objective measure of involvement of the CNS to be communicated to the patients and families.

While genetic diagnoses remain the ultimate end of the diagnostic odyssey in mitochondrial disorders, brain MRI plays an important role in shortening and finetuning this process. Our data (chapter 4) suggests ways to differentiate mitochondrial disorders from other neurometabolic disorders through specific findings on MRI, thereby helping the physician to target the genetic investigations and management , which is especially important in the many countries, where whole exome sequencing is not the diagnostic standard yet. The correlations described in the thesis help to direct the genetic testing and suggest the genes of interest thereby reducing the turn around time for targeted or exome sequencing. MRI also helps to define the phenotypes in individual patients better, thereby providing the valuable corroborative evidence for the potential pathogenic variants identified in exome sequencing studies. This in turn helps to reduce the cost of investigations and will be of direct benefit to patients and patient's families.. The exact economic impacts of these findings are difficult to ascertain, but it reduces the time to diagnosis considerably.

Defining the course, prognosis and treatment

As discussed in the thesis (chapter 7), defining the prognosis and course at a given point of time is the biggest challenge faced by the physician. The disease course largely depends on the organ system involved with the nature of the genetic variations being an important factor. We show in the thesis (chapter 5&6) that the MRI phenotype might be used in the prognostication of mitochondrial disorders. Our data showed that certain MRI phenotypes such as leukoencephalopathy is associated with a better prognosis. It also showed that presence of additional lesions on MRI such as brain stem signal changes might decide the outcome in individual patients (chapter 2). As noted in the thesis "MRI, because of its non-invasive nature and the ability to define the anatomical pattern of brain injury overtime can play an important role in predicting the clinical course and monitoring treatment response in individual patients." Most importantly, we expect that our work will pave the way for the use of MRI in natural history studies. This has implications for patients and

patient organizations in view of the objective nature in which the information can be communicated to the patients and their families.

One of the biggest challenges in developing a clinically relevant treatment strategy in mitochondrial disorders is lack of objective and validated outcome measures.[6] Our data advocate the use of MRI. The outcome in certain mitochondrial disorders tends to correlate with the structural changes on MRI and there is an apparent convergence at the level of MRI findings even when the genotypes are different. It would, therefore, be an attractive option to construct MRI homogenous groups for clinical trials. So far, MRI has not been included as an outcome measure in mitochondrial treatment trials. Since the inception of this study another group has developed and validated a scoring system for MRI in mitochondrial disorders which can be used for rating disease progression and outcome after intervention in clinical trials.[5] In this way, the studies presented in this thesis have broader implications for pharmaceutical companies, involved in the development of new therapies and drug trials.

In addition to the role of MRI in facilitating prognosis and therapy, we also examined three important neurological features in mitochondrial disease which include peripheral neuropathy, epilepsy and leukoencephalopathy. All the three features are important factors leading to chronic disability in mitochondrial disorders. Epilepsy is one of the key manifestations of neurological diseases caused by pathogenic mutations in many genes affecting mitochondrial function.[7] It is one of the important features limiting the quality of life in many mitochondrial disorders especially MERRF and MELAS syndromes.[8] In addition secondary mitochondrial dysfunction has been described in various epileptic disorders.[9] Epilepsy being one of the common problems faced by the neurologist, characteristics of epilepsy associated with mitochondrial dysfunction improve both evaluation and management. The analysis of course and prognosis in relation to phenotype, genotype and MRI findings after a long period of follow up is one of the strengths of this thesis. Our data describe the most commonly used medications and the therapeutic response in specific subsets of patients and could be converted into management guidelines in mitochondrial epilepsy.

A potential relationship between immunological activation and mitochondrial dysfunction (chapter 6) in mitochondrial leukoencephalopathies is a relatively unexplored domain of mitochondrial medicine. Eventhough this has been suggested before, especially in multiple sclerosis and related disorders and LHON-MS, we have demonstrated that immune activation does exist in primary mitochondrial disorders. This has been amply substantiated by the MRI findings and therapeutic response to immune suppressive agents and a long-term follow up. These findings have implica-

tions for the treatment of mitochondrial disorders, bringing out novel options, which has implications for the mitochondrial community as a whole and can contribute to the development of management guidelines in patients with mitochondrial leukoencephalopathy.

References

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