Brain MRI in Mitochondrial Disorders

Summary

Magnetic resonance imaging has been used extensively in the evaluation and follow up of neurometabolic disorders especially mitochondrial disorders. It offers a non-invasive way of assessing the structural, functional and metabolic state of the central nervous system and an easily available diagnostic modality in the early stages of evaluation. There are only few large studies, which focus on the magnetic resonance imaging findings in patients with mitochondrial disorders. More importantly the therapeutic and prognostic implications of specific MRI findings in routine clinical practice remains largely unexplored. Moreover the role of MRI in defining the phenotypes thereby providing valuable corroborative evidence for the potential pathogenic variants identified in exome sequencing is also emerging. With this background the study aimed to explore the prognostic and therapeutic significance of MRI findings in mitochondrial disorders. We studied the phenotype genotype correlations with special reference to MRI findings in specific subsets of mitochondrial disorders in order to guide prognosis and therapy [**chapter 2**], correlated peripheral neuropathy with underlying genetic defects [**chapter 3**], evaluated if specific imaging findings can discriminate mitochondrial disorders from other metabolic disorders [**chapter 4**], analyzed MRI findings in specific subset of patients to find out factors which can predict prognosis and monitor therapy [**chapter 5&6**]. **Chapter 7** discusses the relevance of the findings in a broader perspective of application in the clinical practice and future research.

Chapter 1 is introductory and reviews the current literature on the MRI findings in various mitochondrial disorders. The MRI findings of mitochondrial disorders in the context of ever expanding genotypes in the era of next generation sequencing were studied. Most of the studies report the cross sectional findings and detailed descriptions are lacking. Inspite of the myriad of genes and variations involved, the chapter demonstrated the convergence at the level of MRI findings amidst the clinical heterogeneity. The findings mainly converged to three important groups viz.bilateral symmetrical involvement of deep ganglionic structures suggestive of Leigh and Leigh like syndrome; leukoencephalopathy and stroke like lesions. In **chapter 2**, we analyzed the MRI findings in detail in a cohort of genetically defined patients with mitochondrial disorders. The study gives a detailed description of the anatomical pattern of CNS involvement identified by routine MRI sequences such as T1W, T2W and FLAIR sequences and the findings on various quantitative MR imaging studies such as DW1, MRS and SWI. Even though the study included only a limited number of genotypes it brought out a detailed description of the structural alterations in three different genotypes of mitochondrial disorders. Analysis of the special sequences revealed, basal ganglia mineralization, lactate peak on magnetic resonance

spectrometry and diffusion restriction reflecting the various pathophysiological processes in these patients. Comparison of the magnetic resonance imaging findings in the three groups showed that cerebral atrophy and cerebellar atrophy, cortical signal changes and basal ganglia mineralization were seen mostly in patients with mitochondrial mutations. Brainstem signal changes with or without striatal lesions were characteristically noted in *SURF1* group. There were no consistent MRI findings in patients in *POLG1* group. The value of MRI based phenotypic characterization in non-syndromic mitochondrial disorders also has been emphasized in this chapter. The specific tract involvement of spinal cord in a patient with primary LHON mutation and identification of a mitochondrial variation in infantile onset basal ganglia stroke syndrome and mineralizing angiopathy are noteworthy. Follow-up images in a limited number of patients revealed that the findings are dynamic and revealed either progressive atrophy or involvement of new anatomical areas emphasizing the need for regular follow up evaluations. Next in **chapter 3** we studied genetic basis of peripheral neuropathy in mitochondrial disorders and established correlations. Axonal neuropathy involving either sensory, motor or sensory motor nerves was the commonest nerve conduction abnormality identified. A demyelinating neuropathy was seen predominantly in patients with *SURF1* mutations. Neuropathy was subclinical in majority of the patients and helped defining the multiaxial nature of the disease. It is intriguing to note the differential involvement of axons and myelin in mitochondrial disorders and their relationship with specific genetic variations. Even though the axonal involvement can be explained based on the chronic energy deprivation theory, the involvement of myelin especially in those with *SURF1* variations is fascinating. This calls for more detailed studies to interrogate the interrelationship between *SURF1* and peripheral myelin integrity.

In addition to studying the phenotype genotype correlations we also evaluated the role of specific MRI findings in differentiating mitochondrial disorders from other inherited metabolic disorders [**chapter 4**]. Bilateral symmetrical involvement of the basal ganglia and brainstem defining Leigh syndrome is an important MR imaging phenotype in mitochondrial disorders. Assigning a mitochondrial etiology will facilitate targeted metabolic and genetic testing leading to rapid and specific treatment. In chapter 4 analyses of MRI findings in a large cohort of 125 children with special reference to inferior olivary hypertrophy was done. The study emphasized the presence of inferior olivary involvement in Leigh syndrome secondary to mitochondrial disorders compared to other metabolic disorders. The study also found that that the presence of inferior olivary involvement occurred independently and not always associated with central tegmental tract or dentate nuclei involvement, implying the vulnerability of inferior olivary nuclei to mitochondrial dys-

function. Apart from the role of MRI in defining the phenotype genotype correlations we also examined the prognostic and therapeutic implications of MRI findings in two subset of mitochondrial disorders namely mitochondrial epilepsy and mitochondrial leukoencephalopathies. In **chapter 5**, MRI findings in 27 patients with mitochondrial disorders and epilepsy were correlated with treatment response and long-term outcome. Clinical, genotype and MRI correlations included focal seizures, epilepsia partialis continua, status epilepticus and episodic progression in patients with stroke like lesions and m.3243A>G mutations; progressive degenerative course in patients with cerebral and cerebellar atrophy mostly secondary to m.8344G>A mutation; Chronic progressive external ophthalmoplegia, photosensitive eye lid myoclonus and status epilepticus in patients with normal MRI and *POLG1* mutations; Intermittent partial and generalized seizures in leukoencephalopathy of heterogeneous genetic etiology. The study highlighted that the anatomical patterns on MRI in patients with mitochondrial epilepsy may predict the genotype and phenotypes and recognition of these patterns may help clinicians in prognostication and therapy. In **chapter 6**, detailed analysis of the clinical course, MRI findings and therapeutic response to immunomodulation was performed in 14 patients with mitochondrial leukoencephalopathy. Clinical features which mimicked acquired demyelinating disorder included acute onset focal deficits associated with encephalopathy, febrile illness preceding the onset, unequivocal partial or complete steroid responsiveness, episodic/ relapsing remitting neurological dysfunction and a subsequent stable rather than a progressive course. MRI characteristics included multifocal asymmetric confluent white matter lesions, diffusion restriction, contrast enhancement, spinal cord involvement, and lactate peak on MRS. The study concluded that episodic neuroinflammation is a feature of mitochondrial leukoencephalopathies which may overlap with that of acquired demyelinating disorders in children. The response to immunomodulation was noteworthy and the therapeutic implications of these observations need to be explored in further studies. **Chapter 7** discusses the relevance of our findings in the current scenario of paradigm shift in the diagnostic evaluation of mitochondrial disorders brought out by next generation sequencing. The chapter emphasizes the need for incorporating MRI studies in natural history studies. It also discusses the hitherto unexplored field of application of MRI findings in prognostication and therapy of patients with mitochondrial disorders and brings out avenues for future studies. **Chapter 7** also discusses the emerging treatment options in mitochondrial disorders and the role of MRI in guiding and monitoring treatment response.

In this thesis, application of routine MRI in diagnostics, mainly based on phenotype genotype correlations has been studied in addition to its application in prognos-

tication and therapy in limited subsets of patients. It is envisaged that extension of these studies to more subgroup of patients and the systematic application of advanced imaging techniques may bring out new avenues on the role of MRI in management of patients with mitochondrial disorders. These studies should lead to the routine and methodical use of MRI in natural history studies and also therapy monitoring.