

Proceedings of the UK Histiocytosis Forum 2015

The First UK histiocytosis Forum took place at the Thackray Medical Museum in Leeds on 21st October 2015. Approximately twenty-five physicians and scientists attended from all over the UK. A special theme of the meeting was the diagnosis and management of pulmonary LCH and chest physicians Jay Suntharalingam and Rebecca Mason from Bath and Simon Johnston from the National Centre for Lymphangiomyomatosis in Nottingham were present. There was also a notable presence from UK dermatologists; Chris Dobson from Lancashire, Muzlifah Haniffa from Newcastle and Catherine Brorysiewicz from Imperial.

Pathogenesis, molecular pathology and radiology

In the first session, Matthew Collin (Newcastle) gave an overview of the pathogenesis of LCH and ECD, the involvement of different kinase gene mutations and the differences between multi-system and single system disease. In addition to BRAF V600E, a large range of mutations and gene fusions involving the MEK/ERK and mTOR pathways have now been described. MEK/ERK pathway mutations tend to favour LCH while mTOR pathways are more frequently involved in ECD, although just over half of all LCH and ECD patients have BRAF V600E. Mutation detection in bone marrow, peripheral blood or urine allows diagnosis in many patients with multi-system disease but is much less sensitive in single system disease.

Reuben Tooze (Leeds) then presented a talk on the pathology of histiocytic disorders. He also emphasized the importance of genetic testing in the diagnosis of histiocytosis, especially in ECD where pathological findings are frequently non-specific and in difficult cases where access to targeted therapy may prove life-saving. Most centres have access to BRAF V600E testing and MAP2K1, PI3K and RAS testing are currently being piloted. A notable exception is pLCH in which a radiological diagnosis is often sufficient and tissue samples are now rarely taken. Catherine Borysiewicz (Imperial) mentioned that broncho-alveolar lavage can be helpful in monitoring airway CD1a+ cells that are presumably LCH cells.

Chirag Patel (Leeds) reviewed the radiology of histiocytosis making the important point that LCH radiology is often 'characteristic' and helpful in arriving at a diagnosis. ECD radiology is even more specific and several findings such as long bone sclerosis, hairy kidney or aortitis can be pathognomonic. This is especially useful given that ECD pathology is often not informative. Matthew Collin asked about the availability of volumetric brain MRI for assessing grey matter decline but Chirag replied that this would not be routinely done when assessing the pituitary bright spot or mass lesions within the brain. A discussion ensued on the timing of PET-CT in assessing disease response and it was agreed that this was therapy dependent. Targeted treatment with BRAF inhibitors may have very rapid effects within 4 weeks while anti-inflammatory therapy with methotrexate or interferon could take up to 6 months to reach a plateau.

Clinical experience

In the second session, Vasanta Nanduri (London) opened with a comprehensive description of paediatric LCH, including late effects and the current international treatment protocol LCH IV. Survival of children with LCH has improved markedly over 2 decades without any change in the standard treatment of prednisolone and vinblastine. The use of novel agents was discussed in paediatrics but barriers of potential toxicity are considerable compared with the use of these drugs in adults. In the current treatment trial there is also no routine provision for molecular diagnostics although this may be conducted as a parallel research study, pending the results of applications to Bloodwise and CRUK for funding.

Catherine Borysiewicz (Imperial) gave a long awaited summary of the Hammersmith Histiocytosis Clinic activity. She presented a subset of data from 312 patients and described the initial work up of patients which included a comprehensive clinical assessment. Approximately 50% of adult patients had presented at a median age of 40-50 years with multisystem involvement requiring systemic therapy. Azathioprine was the most frequently used systemic therapy followed by escalation to cladribine. VP16 had been used in the past but there was no experience of cytarabine. An interesting subset of patients with severe pLCH had come via the Brompton Hospital and had been treated aggressively with cladribine. The utility of this drug to arrest pLCH is unproven in large clinical trials and a report of this cohort will be very interesting.

Peter Hillmen (Leeds) presented a recommendation for the clinical evaluation of adult histiocytosis patients with an emphasis on molecular diagnosis and the importance of PET-CT. In addition to clinical examination, endocrinology, respiratory function testing, cardiac evaluation and brain MRI are required in most patients. He went on to show the dramatic efficacy of vemurafinib in a number of patients with BRAF mutated ECD. Tahla Munir (Leeds) followed with a presentation on the utility of weekly methotrexate (10-40mg) in patients with LCH and ECD. Toxicity was minimal with only mild liver enzyme rises and no cytopenia. Chris Dobson (Lancashire) commented that toxicity might be different according to a particular patient group. Psoriatic patients have a higher risk of liver toxicity than rheumatology patients and it was suggested that fibroscans might be used to screen histiocytosis patients on MTX, in the absence of extensive experience. So far, the pilot data are encouraging in terms of response with nearly 80% of patients achieving a PET-CT response and approximately one-third achieved remission. There is currently no experience of hydroxycarbamide for treating histiocytosis in the UK.

Rebecca Mason (Bath) gave the final talk presenting a review of pLCH in the UK achieved through a rare disease registry of the British Thoracic Society. She recorded over 100 cases of which more than half were available for follow up. The picture emerged that pLCH has little overlap with multi-system LCH. Approximately half of patients improved with smoking cessation and inflammatory changes can resolve completely. Rare patients (<5%) developed diabetes insipidus or evidence of other organ involvement. A small number also had inexorable respiratory decline and were referred to specialist centres for systemic therapy.

Summary and priorities for service development:

- Opening of the European Adult Histiocytosis and Global Erdheim Chester Disease registries in the UK. This will require an application to IRAS for ethical approval to be led by Matthew Collin and Johan Visser (Leicester).
- Writing of guidelines for the management of adults with histiocytosis in the UK, for example through the British Committee for Standards in Haematology to be led by Peter Hillmen, Tahla Munir and Matthew Collin
- Pursuit of a molecular diagnosis in as many patients as possible through local pathology laboratories and referral to specialist centres for allele-specific PCR or next generation sequencing. Most centres can access BRAF V600E testing as this is frequently used in melanoma. Leeds Haematology Malignancy Diagnostic Service also offers clinical MAP2K1 testing
- Study of the use of PET-CT and radiological findings in adults with histiocytosis in the UK led by Chirag Patel
- Study of the use of methotrexate in adults with histiocytosis by Peter Hillmen and Tal Munir