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Editorial Comment

Cognitive deficits in patients with multisystem Langerhans cell histiocytosis—a commentary

Langerhans cell histiocytosis (LCH) is regarded as a continuum of clinical entities ranging from a localised lytic bone lesion to a fatal disseminated myeloid leukaemia-like entity. The treatment of LCH depends on the severity of disease and ranges from local corticosteroids to multi-drug chemotherapy. In general, a high percentage of 'cured' LCH patients have highly debilitating late sequelae from their disease [1].

The unique pathological picture of LCH combines features of carcinogenesis and chronic inflammation, and is caused by an uncontrolled local or disseminated pathogenic clonal proliferation of dendritic cells (DCs) with Langerhans cell (LC) characteristics [2]. The LCH cells are arrested in an immature, partially activated stage, and show a deviant regulation of cell division [3]. Their aberrant interactions with T cells and the lesional microenvironment are typified by the high level production of diverse cytokines, creating a true 'cytokine storm' [4]. These cytokines (and chemokines) are mitogenic and/or chemoattractants for other cells like macrophages, granulocytes and lymphocytes, resulting in an amplification cascade, with cytokine upregulation in auto- and paracrine loops. The resulting chemokine imbalances form the basis for the blockage of the maturation of the CD1a+ LCH-cell in the LCH lesion [5]. Chemokine and chemokine receptor patterns might also explain LCH predilection sites and lesion composition, that are reminiscent of those observed following chronic granulomatous inflammation. These factors potentiate proliferation and growth. Associated pathogenic effects include systemic manifestations such as macrophage activation [6] and fever, as well as fibrosis, necrosis and osteolysis. We believe these high and unbalanced levels are the basis for the pathophysiology of the LCH lesions. As such, neuronal injury can be expected, as we know that either high levels and/or an altered balance of pro- versus anti-inflammatory cytokines can cause neuronal damage.

The vast amount of research over the last decade has clearly improved our understanding of the basic science of LCH, the LCH-cell and its normal counterpart the LC, and this ultimately leads to a better understanding of the clinico-pathology of LCH.

The endeavours of physicians and other investigators over the last two decades to work together within the international Histiocyte Society have established standardised nomenclature, clinical and pathological criteria [7,8]. This standardisation of nomenclature and the development of one "histiocytic language" has made it possible to accumulate and record coherent data. It has also allowed the initiation of co-operative international studies of the natural evolution of LCH and its response to treatments [9]. As such, shared information has led to the development and participation in international studies and treatment approaches. Prospective controlled clinical trials with quality assurance and proper statistical analyses [10], in combination with an improved knowledge of the pathophysiology should ultimately lead to better treatments and improved patient outcome. This should allow late effects to be studied [11].

A single institution study on these late effects was undertaken by Dr Nanduri and colleagues and their results recently reported in their manuscript entitled: "Cognitive outcome of long-term survivors of multisystem Langerhans cell histiocytosis: a single-institution, cross-sectional study" [12]. They demonstrated significant deficits in 28 long-term survivors of multisystem LCH. In a systematic assessment of this cohort, cognitive function was tested in a very elegant manner, using a variety of primarily age-appropriate Wechler-based tests. The research group led by Dr Vargha-Khadem has a great deal of experience in the paediatric population, especially in patients with acute lymphoblastic leukaemia [13,14].

Not surprisingly, in the 8 patients with proven Central Nervous System (CNS) involvement (patients with either clinical neurological abnormalities and/or magnetic resonance imaging (MRI) involvement) clear neuropsychologic deficits were recognised. In other words, the clearly CNS damaged patients had severe deficits in intelligence, memory and learning, language and academic achievements. The psychological, behavioural and educational problems in this group were mild to severe, but 6 of them (75%) require special schooling. However, of special interest were actually those patients

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without clear CNS damage by either neurological examination and/or on MRI scanning ($n = 20$). In the patients without neurological or behavioural abnormalities and with or without diabetes insipidus (DI), the mean intelligence quotient (IQ), based on a combination of Verbal IQ, Performance IQ and Full Scale IQ, was not significantly different from the mean of the population. Nevertheless, the wide variation in results—as shown by the large standard deviation observed for most of the cognitive items studied—indicated that there were isolated patients with cognitive deficits. As a result, the authors very appropiately emphasise that an early assessment should be undertaken in every patient with LCH and not only those with obvious CNS disease.

The outcome of "basic" neuro-psychological tests in all patients with LCH, opens the way for communication, through the parents, with the schools of these patients. Therefore, it is essential that the physician involved in the care of LCH patients ensures there is good communication between parents and the school. Subsequently, the school can contact the physician for additional and specific information leading to possible direct interventions and support. Remedial teaching, extra individual instructions and extra study time may lead to improvements.

In conclusion, collaborations between researchers and physicians over the years within the histiocytosis world have paved the way for a basic understanding and treatment of patients with LCH. This has resulted in better recognition and, where possible, treatment of late effects, especially severe ones like cognitive deficits. The key point demonstrated in the aforementioned study is that the physician treating patients with LCH should be aware of those patients without "clear" CNS abnormalities, but where the cognitive deficits might be so subtle that they can only be determined using specialised testing. Such testing could lead to improvements in the quality of life of the individual LCH patient.

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