

Editorial

The Impact of Molecular Diagnostic Techniques in Paediatric Pathology: Transforming the Diagnostic Landscape

In recent years, significant advances have been made in the accuracy, availability and feasibility of applying molecular techniques routinely for diagnostic purposes. Whilst such technical developments have wide ranging implications across the field of diagnostic pathology, paediatric pathology in particular is becoming revolutionised by the consequences of these new approaches. Many entities encountered by paediatric pathologists either represent primary disorders of development, many of which have underlying genetic aetiologies, or secondary disease, such as embryonal-type malignancies, which are often associated with specific and pathogenic underlying chromosomal or genetic changes. Furthermore, recent understanding of the underlying molecular genetic mechanisms of a range of diseases has resulted in the development of novel approaches both to diagnosis and even classifications of entire disease areas.

In this special issue, examples of the effect of molecular genetic findings across a range of conditions in paediatric pathology are presented. Most paediatric solid organ malignancies represent embryonal or blastemal type tumours, which often recapitulate stages of embryonic development, and many of which are now associated with underlying genetic changes which can be detected and used diagnostically. This approach allows highly accurate diagnosis on tiny samples of tissue through the use of techniques such as fluorescence in-situ hybridisation (FISH) and polymerase chain reaction (PCR), and future application of techniques such as microarray profiling to such samples is likely to provide prognostic and therapeutic information, in addition to specific diagnosis. This change in diagnostic approach to tissue samples has also resulted in the increased feasibility of less invasive clinical approaches to the investigation of such lesions, such as primary diagnosis by percutaneous needle biopsy.

Cardiomyopathies, broadly defined as primary intrinsic cardiac muscle disease, in childhood represents a range of conditions, with differing clinical and morphological features. Nevertheless, an increasing number of such conditions is now recognised as being associated with specific underlying genetic changes, which have affected both the approach to their diagnosis and investigation, and also to implications for other family members. For example, most cases of idiopathic hypertrophic cardiomyopathy are now known to be caused by mutations in the genes encoding structural proteins of the contraction apparatus of the cardiac myofibre and arrhythmogenic right ventricular cardiomyopathy is associated with mutations of desmosomal junction-associated proteins such as desmoplakin, plakoglobin, plakophilin, desmocollin and desmoglein. The histiocytoses represent a clinically diverse group of conditions characterised by abnormal proliferation and tissue infiltration by histiocytic cells. Recent basic science advances have characterised the mechanisms and pathways by which such cells proliferate and differentiate, leading to conceptual changes in the way these disorders are viewed.

Paediatric renal tumours represent the commonest group of non central nervous system paediatric soft tissue tumours. Specific genetically distinct subtypes of paediatric renal cell carcinoma have been identified, which in some cases has allowed specific diagnosis based on targeted immuno histochemical staining, such as nuclear TFE3 expression in Xp11.2 associated renal cell carcinoma. Furthermore, recent molecular genetic studies have begun to provide more information regarding the genetic process linking nephrogenic rests and nephroblastoma, and relation to clinical behaviour. The ultimate aim of such molecular understanding is not simply more accurate and rapid diagnosis, but ideally the development of more effective and targeted therapies. One such area in which basic science understanding of tumourigenesis is leading to specific targeted therapies is in the area of modification of host-tumour response, generically termed tumour immunotherapy. It appears that specific genetic alterations in some tumours may attenuate the host immune response, allowing tumour growth and spread, but also providing potential novel therapeutic targets for development of future therapies.

Paediatric bony lesions may cause many diagnostic problems for pathologists, especially biopsy samples. Many lesions may be associated with underlying genetic syndromes and particularly troublesome differential diagnoses are now much easier since the recognition that certain entities are associated with specific molecular changes, detectable by PCR on paraffin-embedded tissue samples. An obvious example is the molecular distinction between head and neck fibro-osseous lesions, especially the differential between ossifying fibroma and fibrous dysplasia (FD); in both syndromic and non-syndromic forms, many cases are associated with a point mutation involving the GNAS1 gene, located at 20q13.2. This diagnosis may have other implications for future patient management. Similarly, our understanding of the underlying pathophysiological mechanisms of paediatric conditions which may predispose to disease in later life is beginning to increase and this area is likely to become of greatly increased importance in coming years. For example, metaplastic changes in the oesophagus related to gastro-oesophageal reflux, known as columnar-lined oesophagus or Barrett's oesophagus, are relatively rare in childhood but there is an association with subsequent development of dysplasia and adenocarcinoma in adulthood. The process may involve genetic instability and loss of p16 tumour suppressor function as primary events in the neoplastic progression.

It is not only paediatric surgical pathology where molecular diagnostic testing is changing practice, but also autopsy pathology, especially for investigation of the causes of sudden unexpected deaths, and this area in particular is likely to change dramatically in future, with resulting changes in the entire perception of the role and technique of autopsy. An increasing

number of underlying metabolic conditions are recognised, in addition to traditionally recognised fatty acid oxidation disorders, it is possible that genetic differences in host responses to microbiological agents may manifest as infant death and conditions associated with cardiac arrhythmias but no structural abnormalities such as long QT syndrome, may become of increasing importance. Similarly, perinatal autopsy practice is changing with molecular testing allowing diagnosis of specific genetic disorders based on routine histological sampling and even certain placental disorders are increasing as associated with specific maternofetal genotypes, such as conditions associated with maternal or foetal thrombophilic disorders and mosaicism.

In summary, the practice of all aspects of paediatric pathology is rapidly becoming revolutionised by the impact of molecular genetic advances, both technical and conceptual. This special issue will provide an overview and some specific examples of currently topical areas in which practice is changing in the 21st century.

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