ASK THE EXPERTS

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CNS Oncology

Magnetic resonance spectroscopy and beyond for pediatric brain tumors

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Q How frequently are brain tumors diagnosed in children? Historically, how were they diagnosed?

Approximately one in 3000 children will develop a brain tumor and this represents about a quarter of all children who develop cancer. Brain tumors are the most common cause of cancer death in childhood and new advances are needed to improve their outlook. One of the problems is the length of time it takes from first symptom to diagnosis, which is often several weeks and can be many months. Presenting symptoms such as headaches, vomiting and even squint are common in children and the lack of a rapid, easily accessible, cheap diagnostic test often conspire to ensure that the diagnosis is not made promptly. When there is clinical suspicion that a brain tumor exists, cross sectional imaging is undertaken. Initially this may be with a CT scan but the gold standard is MRI. This investigation provides detailed images of the tumor and its relationship to surrounding structures. Definitive diagnosis requires a tumor sample to be obtained at operation leading to further delay whilst this is arranged and samples are processed all of which can take several days.

Q How does Magnetic Resonance (MR) spectroscopy work and what does it show? How does it differ from MRI?

Magnetic resonance spectroscopy can be performed during the MRI scan using the same scanner. MRI provides an image of the structures present, largely by measuring

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water levels. MR spectroscopy differs in that it gives a chemical profile of the tumor. The main chemicals that are measured by MR spectroscopy are small metabolites and many of these have been related to important cellular processes in cancer. Choline-containing metabolites are related to cell growth and division and have been correlated to mitosis and Ki67 index. Choline kinase is now a drug target indicating the importance of this molecular pathway in cancer. Creatine is involved in cell energetics as are glutamate and glutamine. N-acetyl aspartate is the most abundant metabolite in brain being present in normal neurons and is reduced in tumors. Mobile lipids can also be detected and have been related to apoptosis and necrosis. So, whereas a relatively small number of chemicals can be detected currently using MR spectroscopy, many of those measured have an important role in cancer.

Q What benefit does MR spectroscopy have for the patient?

It has been recognized for many years that the chemical profiles of tumors measured by MR spectroscopy differ from normal brain and that one tumor type differs from another. Using this information for noninvasive diagnosis has therefore been a focus of attention. Certain metabolites are highly suggestive of specific tumors but more commonly radiologists use the visual patterns of the various metabolites to help propose a diagnosis. More sophisticated aids to interpretation of MR spectroscopy are also becoming available. Improved noninvasive diagnosis allows earlier planning of treatment, better informed surgery and more timely discussions with the families. This diagnostic potential can be particularly useful for discriminating relapse from treatment-related damage, a particular challenge that is becoming more common as intensity of treatment increases [1]. In addition to noninvasive diagnosis, there is increasing evidence that certain metabolites provide novel biomarkers of patient survival [2]. We know that two patients with the same histological diagnosis and the same treatment can respond in very different ways and new biomarkers that can allow us to personalize treatment are desperately needed. MR spectroscopy can provide these in a noninvasive manner. There is also evidence that in some cases MR spectroscopy can give information on the early response of tumors to treatment.

Q Are there any risks involved in MR spectroscopy?

MR spectroscopy has no known risks above and beyond those of conventional MRI, which in itself is very safe when used with the appropriate precautions. Some children will not be able to have MRI scans, mainly those with pace makers or certain metal implants. In addition, MR spectroscopy is very sensitive to artifacts produced by metals and sometimes it is not possible to collect reliable scans on children with metal implants. Dental braces can be a particular problem leading to uninterpretable data being collected from some regions of the brain.

Q How will MR spectroscopy compliment other imaging techniques in diagnosing pediatric brain tumors?

Whilst MR spectroscopy has an impressive record in noninvasive diagnosis, in practice, doctors make decisions using all the information they have available. In particular, there are other MRI-based methods that investigate the properties of tumors. As a group we usually call these techniques functional imaging [3]. Diffusion-weighted imaging gives information on tumor ultrastructure and in particular cellularity. Diffusion tensor imaging can be used to image nerve tracts and see whether they are invaded by tumor. Perfusion imaging measures the blood flow within the tumor and can give information on blood vessel properties such as permeability. These techniques are complimentary and combining them allows us to build up a more complete picture of the tumor and its properties. With improvements in technology we can now perform all of these techniques in the same scan to provide what we call multimodal imaging.

Q Is this diagnostic tool being translated to other centers? Do you think it will become common practice to utilize MR spectroscopy in the clinic?

Little has been achieved if a technique can only benefit those who attend one center and the dissemination of techniques across multiple centers is essential. In the UK we have a network of centers that are committed to the development, implementation and evaluation these techniques. Advances made in one center can be rapidly disseminated to the other centers and problems with multicenter use identified at an early stage. In rare diseases such as childhood cancer,

new techniques can only be tested on sufficient numbers if multicenter studies are undertaken. Recent multinational studies have indicated that around 50% of centers treating children with brain tumors routinely use MR spectroscopy. So the technique is being widely used. The challenge is to provide the radiologists with tools that can help them to interpret the data. Such clinical decision-support systems exist but have not yet been developed to an extent where they are ready for widespread use in routine clinical practice.

Q What can you tell me about current clinical trials involving MR spectroscopy and pediatric brain tumors?

One of the main aims has been to develop and evaluate a clinical decision support tool for the noninvasive diagnosis of children's brain tumors based on MR spectroscopy. A multinational study that combined MR spectroscopy with pattern recognition software has just reported high levels of accuracy for the diagnosis of the main tumor types [4] and is undergoing further clinical evaluation. In the UK there is a study called "functional imaging of tumours" which is collecting multimodal MRI data including MR spectroscopy over a network of centers. More than 700 children have been enrolled on the study which aims to develop and evaluate functional imaging for the improved diagnosis, management and understanding of childhood cancer. MR spectroscopy is also being incorporated in treatment trials and the International Society of Pediatric Oncology Europe is agreeing multimodal protocols for use in multinational clinical trials. MR spectroscopy is also part of the multimodal imaging protocol for HERBY, a trial of bevacizumab in high grade gliomas of childhood.

Q What do you see as the key goals and challenges for imaging in the diagnosis and management of pediatric brain tumors in the next 5 years?

The key challenge for imaging is to move away from the subjective visual interpretation of images to the use of reproducible quantitative measures. This will require the agreement of protocols that can provide comparable data from multiple scanners; a rigorous system for quality control that can be implemented across different centers; agreed data formats that allow data to be transferred and analyzed centrally and the development of analysis software that meets regulatory requirements and can allow for the differences in acquisition protocols that inevitably occur from multiple centers. These are significant challenges that will require close collaboration between scientists, clinicians, scanner manufacturers and other commercial enterprises. The benefits will be a modernized imaging platform which will use these modalities to their optimum for the benefit of the patients.

Disclaimer

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