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Commentary

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CONCEPT OF GLIOMAS

In the update on paediatric gliomas, the authors have succinctly summarised the current state of knowledge about this large group of tumours. However, I would question the wisdom of focusing such an article upon such a large and diverse group of tumours which are linked only by their capability to express glial markers. This grouping includes all the major categories of brain and spinal tumour with the exception of the embryonal tumours, meduloblastoma/PNET (primitive neuro-ectodermal tumours). Glial cells are a ubiquitous cell category within the central nervous system which have the potential to express a very large variety of phenotypes; they undergo massive proliferation during the fetal, postnatal and childhood phases of brain growth and are inevitably involved in the processes of both malignant and reactive cellular proliferation within the brain. This, coupled with their widespread anatomical distribution, means that they are the largest target cell group to be involved either in the initiation of tumorigenesis or as a bystander to the process. Whether this collective category has any great value to anyone, other than the neuropathologist, is doubtful. Indeed the process of aggregating this diverse group of entities serves to distract the reader from the individual categories, masking the detailed knowledge we now have. If a collectivist approach is to be taken then an anatomical categorisation might be preferable as the location of the tumour determines the symptoms, the surgical options, the planning of the radiation fields, the risks and consequences of neurological damage and dictates the type of arrangements that will be necessary for rehabilitation. To switch immediately to an anatomical classification may pose difficulties as it would go against the current belief that biological investigation will reveal much about tumour behaviour and be the key to unlocking novel approaches to therapy. It would be my suggestion that modern day paediatric oncology practice should at least give the five major categories of childhood brain tumour (astrocytic low grade, astrocytic high grade, brainstem glioma, ependymal and embryonal tumour) equivalent independent status to other solid tumour groups and then group them together under the overall heading of brain and spinal tumours because they are cared for by a separate group of neurological specialists using treatments designed to be applied to the brain. The location of the tumours means that neurological injury is a substantial risk justifying a special set of attitudes to decision making, delivery of treatment and arrangements for rehabilitation and follow-up [1].

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AETIOLOGY AND PREDISPOSITION SYNDROMES

'What caused my child's brain tumour?' is probably the most frequently posed question by parents who have just been informed of the diagnosis. Rising incidence rates are often quoted in countries with good cancer registration. The strongest candidates for aetiological agents include environmental exposure to electromagnetic fields [2, 3] and nitrosamines as well as previous exposure to therapeutic radiation. Preliminary results from the recent IARC study of childhood brain tumours does not confirm an enhanced risk related to nitrosamine exposure (Ken Muir, IARC, Lyon, France). The U.K. National Case–Control Study has collected 5 years worth of cases of all paediatric cancers detailing family medical and occupational histories, measurements of environmental exposure to electromagnetic fields and radon gas levels within the home. The study also obtained tumour material and blood from each case. We must await the outcome from this study to see if electromagnetic fields and environmental radiation are still seen to play a part as this is probably the largest study of its type. Unfortunately, recruitment of cases with brain and spinal tumours were significantly less than those for leukaemia lymphoma and may have been insufficient to address any single environmental exposure question. It likely, therefore, that new specific information about the aetiological factors is likely to be a long time coming.

Genetic predisposition to tumour formation is of great importance for those individuals with neurofibromatosis type 1 (NF-1). It should be emphasised that 4–7% of individuals with NF-1 will get a symptomatic brain tumour. Optic chiasm and optic nerve tumours predominate and the risks of tumours occurring elsewhere are only four times that of the normal population [4]. Where a tumour has occurred, then the individual must be assessed and treatment considered with great care as there are a wide range of innocent scanning abnormalities which may be unrelated to presenting symptoms and may resolve spontaneously [4, 5]. Toxicity of any treatment must be judged against the background of a child who may already have neurodevelopmental problems related to NF-1 and may be vulnerable to enhanced neurotoxicity of treatment, particularly radiotherapy [6, 7].

Tuberous sclerosis is associated with the presence of intracranial space-occupying lesions called tubers. These must be included in the differential diagnosis of any space-occupying lesion, but once the genetic disorder is identified they are no longer the province of the neuro-oncology team as aggressive antitumour treatments are rarely indicated, although surgical management of hydrocephalus is necessary in some cases.

SYMPTOMATOLOGY

Symptoms which herald a brain tumour are dictated by a combination of the presence or absence of raised intracranial pressure and the anatomical location of the tumour [8, 9]. Within all childhood cancers, brain tumours are noted to have the longest lag time between symptom onset and diagnosis [10, 11]. This situation frequently means that more than one doctor has been consulted prior to a diagnosis being made and leads to great dissatisfaction in many families. In general where there is sudden onset of symptoms of raised intracranial pressure, the diagnostic scan is ordered. Where the symptoms of raised intracranial pressure are less notable and particularly where they are fluctuating in severity and associated with disturbances in behaviour, mood, growth and development, it can take some time before the 'penny drops' and a scan is ordered.

Do these delays in diagnosis alter the patient's prognosis with respect to both quantity and quality of survival? We would all like to reduce the duration of suffering for the child and family by removing diagnostic uncertainty; this is undoubtedly good medical practice. Tumours which are discovered earlier when they are smaller may be more curable and associated with less long-term neurotoxicity. For those in surgically accessible parts of the brain they may be more resectable as they involve fewer parts of the brain. Radiation fields may be smaller especially with modern computerised planning. Associated hydrocephalus may have been present for less time leading to fewer neurological consequences. In general, malignant tumours are thought to start in one location and subsequently metastasise. Earlier diagnosis may allow the tumour to be recognised before it has disseminated, although this may be a function of the biology of the tumour rather than time. Finally, astrocytic tumours are known to change from 'benign' to 'malignant' both as a function of time and after radiation therapy.

The lag time to diagnosis is, therefore, a major problem which has not been energetically addressed as a specific area for investigation. The greatest attraction is that study in this area has the potential to make a contribution to reducing death rates and improving the health status of survivors without putting them at risk of ever more intensive treatment.

MOLECULAR PATHOLOGY

Better understanding of the biology of tumours is expected to reveal ways of improving therapy. Biological understanding of gliomas lies well behind that of other children's tumours, e.g. neuroblastoma. The biological study of high grade gliomas in adults has been extensive yet has lead to no great breakthrough in treatment. Cokgor and colleagues refer to the expanding knowledge of genetic abnormalities in paediatric gliomas. Interestingly, there is relatively little overlap in the mutations noted in children's tumours when compared with similar tumours in adults. Secondly, there is increasing evidence that similar histologies have different genetic mutations in different parts of the brain. These two observations require a systematic approach to be adopted to the investigation of potential genetic mutations of childhood gliomas. This work should be carried out in collaboration with neuroembryologists as it is only by such a collaboration that the most significant genetic mutations in tumours can be put into context with respect to anatomical distribution and cellular phenotype. Whether this will lead directly to improved treatment is unclear, but similar biological data loss enhanced understanding in other childhood tumours, so there is no reason why this should not be the case in paediatric gliomas.

TREATMENT

Survival rates for paediatric gliomas have not substantially improved in more than two decades [12]. This is in contrast to almost all the other solid tumours of childhood and certainly does not mirror the dramatic changes in outcomes seen in leukaemias and lymphomas. There is no doubt that the brain presents special problems to the oncologists whether he be a surgeon, a radiotherapist or a chemotherapist. One thing is certain, whoever treats these children must be paediatricians in the broadest sense of the word as their clinical needs are wide ranging and can tax the most skilful paediatric team.

Almost all gliomas have improved survival rates with more complete resections. Anatomical location of tumours is critical to surgical resectability. Modern imaging has clarified the anatomical classification of tumours and greatly facilitated the selection of optimal surgical approaches to resection. Nowhere more so than in the brainstem where focal and dorsally-exophytic tumours of the mid brain and medullary cervical region may be resected with good effect, whereas diffuse tumours of the pons and medulla oblongata are generally considered unresectable and tumours of the tectal plate are left *in situ* if the hydrocephalus can be relieved [13].

Radiotherapy is the mainstay of adjuvant treatment for high grade astrocytic tumours and unresectable symptomatic low grade tumours. What is less clear is which of the gliomas require anything more than involved field radiotherapy. Predicting metastasis in gliomas is extremely difficult. It is widespread practice not to irradiate the spine especially in supratentorial tumours.

Chemotherapy has no established role in any glioma. The difficulties of running drug trials in this group of tumours are legion. Having said that, there is now a full range of age specific strategies for the investigation of glial tumours in development in Europe through the activities of brain tumour committee of Societe Internationale d'Oncologie Pediatrique (SIOP). The SIOP infant brain tumour trial recruited all tumour types to a standard chemotherapy schedule using five drugs given on an 8-weekly block using four drug combinations, alternating myelotoxic and non-myelotoxic drugs. This treatment programme was given with the intention of continuing for 1 year or until the third birthday when the patient would be reassessed and radiotherapy given if there was evidence of persistent disease. This study has been closed to patients with PNET because of poor results, but the survival rates for ependymoma is over 50% at 3 years and the small number of high grade astrocytomas have had unexpectedly good results at this stage. The SIOP low grade glioma study stratified treatment by age offering chemotherapy to those with symptomatic tumours who are aged under 5 years, reserving radiotherapy for those who relapse and/or those who are over 5 years of age. Finally, SIOP are just launching an ependymoma study investigating a standardised multidisciplinary strategy aimed at achieving maximal resection with a phase II study of vincristine, cyclophosphamide and etoposide for those patients who have incompletely resected tumours and in whom a response can be observed and a second look operation considered. If this strategy proves acceptable it will provide a framework for the investigation of other

new agents in a phase II setting. High grade astrocytomas and brainstem glioma remain the most problematic tumour groups. There are no known effective drugs. The SIOP are currently considering setting up an international phase II study group network whose intentions are to study new agents in these tumours and develop an international database for control patients for future studies.

CONCLUSION

The authors are to be congratulated on their update, given the complexity of the task. The editors* may wish to reconsider their strategy with respect to brain and spinal tumours and set tasks which fit in with the needs of day-to-day clinical practice. Whether the lack of progress in improving survival rates for this group of tumours is related to an historical lack of clinical trials and a failure to establish multidisciplinary teams expert in neurological care or simply due to a lack of sensitivity to anticancer treatments, is unclear. In the next decade, the results of a range of clinical trials of gliomas will be published; networks of neuro-oncology teams will be established. We must see if the outcome for children will improve, if only by identifying those individuals with tumours sensitive to therapy and delivering it in an optimised manner.

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*Editors comment: In response to Dr Walker' point, there were three reasons for combining brain and spinal tumours in this update. First, space is invariably limited. Second, there is a clear-cut difference (in this Editor's opinion, at least!) between the behaviour of the so-called 'small cell tumours' of the CNS and the tumours of glial origin—the former often disseminate widely via the cerebrospinal fluid, whilst the latter uncommonly do. This difference has direct and major therapeutic implications. Thirdly, the risk of 'over-splitting' a group of rare entities is probably greater than the risk of 'over-lumping' them, especially whilst our ignorance of the underlying molecular pathology is so profound.