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The present and future management of childhood craniopharyngioma

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Abstract Childhood craniopharyngiomas are rare tumours that present formidable difficulties in their treatment if cure is to be achieved without producing severe hypothalamic damage. Experience with our own cases suggests that the morbidity from an attempted radical removal can be predicted – allowing a treatment algorithm to be devised that combines both surgery (radical and "conservative") and radiotherapy (both external fractionated and intracyst instillations) in order to achieve long-term tumour control that is not at the expense of a severe functional disability.

Key words Craniopharyngioma · Childhood · Cerebral tumour

Introduction

Craniopharyngiomas are uncommon tumours. A recent study from the United States [2] suggested an incidence (for adults and children) of 0.13 per 100,000 patient-years – an incidence that does not vary by gender or race. The same authors calculated that 96 childhood cases might be expected out of the total number of 338 craniopharyngiomas predicted for the U.S. each year. Published articles on the subject are unusual if they contain more than 70 cases, and these may have been accumulated over many years. Out of the 75–80 paediatric intracranial tumours referred to our unit each year for primary treatment (as opposed to recurrent tumours and referrals for second opinions) only 3–5 are likely to be craniopharyngiomas.

"Modern" treatment of craniopharyngioma is usually dated from Matson's observation [8] that it was possible at surgery to identify a gliotic "capsule" that capped the tumour and therefore to remove the tumour completely without endangering the hypothalamus. Early enthusiasm for attempts at curative surgery were tempered, however, by the eventual realisation that not only had his tumours not always been completely removed but the patients were often left severely damaged [7]. Recognition of the morbidity of treatment led to a vogue for more conservative methods of treatment – cyst aspiration and radiotherapy, for example.

More recently, the trend – particularly amongst neurosurgeons (to whom these patients are almost always referred in the first instance) – has been towards more radical surgery utilising approaches that reflect advances in surgical technology: the advent not only of the operating microscope but also of instrumentation designed to allow the removal of tumour bulk with as little interference to the surrounding (normal) tissues as possible.

Craniopharyngiomas are (at least at their point of origin) midline tumours that arise either from the pituitary stalk or from the tuber cinereum – the floor of the III ventricle. Each point of origin allows the tumour to ex-

pand in a different way, and thus influences the morbidity (in terms of hypothalamic damage) associated with radical attempts at removal. Tumours that arise from the pituitary stalk typically extend downwards into the pituitary fossa itself – or else expand out from it – that part of the tumour immediately above the fossa possessing as a pseudo-capsule the attenuated dura of the sellar diaphragm. Tumours arising from the tuber cinereum are more likely to extend upwards through the hypothalamus and into the III ventricle.

Of equal importance to the point of origin of the tumour is the degree of involvement of the hypothalamus. Although the tumour may, by histological criteria, be benign, it may still project finger-like processes into the adjacent hypothalamic tissue. Clearly a tumour already involving the hypothalamus through this process of "invasion" is not amenable to a surgical cure without a significant risk that the involved area of the hypothalamus might be damaged.

It is pertinent before discussing management, therefore, to describe the clinical state of a child who has suffered hypothalamic damage (usually in addition to being rendered pan-hypopituitary [4]) as a result of treatment of a craniopharyngioma. At the mildest end of the spectrum is obesity (so-called hypothalamic obesity) – a condition so frequently observed after radical surgery that the parents of a child for whom such an operation is proposed should be specifically warned of its possibility. Obesity can occur with little or no evidence of other cognitive or behavioural problems, but with increasing hypothalamic damage there are worsening learning difficulties associated with defective short-term memory and limited concentration span. The child's behaviour can also be severely affected. Hand in hand with the obesity is a desire to "feed" that may have the child stealing and fighting for food until everything edible in the home has to be locked away. Stealing of anything else that will supply an instant feeling of gratification can also occur. There is also a reversal of the normal circadian sleep patterns [9], which can leave the child awake for most of the night (and on the rampage for food) while during the day he or she can barely be roused. Also, hypothalamic damage can destroy the child's sense of thirst – an essential sensation if the treatment of diabetes insipidus (which if it was not present pre-operatively is almost inevitable following radical surgery) with DDAVP (nasal or oral) is to be successful. The combination of diabetes insipidus and lack of any sensation of thirst leaves children with no idea of when they need to drink, and they therefore swing violently between states of over- and underhydration.

The net result of these disabilities can be a child – perhaps with seriously defective vision as well – whose personality has been completely changed by the combined effects of the tumour and its surgical treatment, who is incapable of normal schooling, whose behavioural problems can have a severe effect upon the family unit and whose life expectancy is shortened because of their vulnerability to a hypothalamically mediated metabolic crisis.

The most common triad of presenting symptoms of a child with a craniopharyngioma is (1) visual failure owing to compression of (in particular) the optic chiasm – but also the optic nerves and tracts; (2) a hormonal disturbance – at presentation most children are likely to be of small stature and have diabetes insipidus (owing to hyposecretion of, respectively, growth hormone and antidiuretic hormone); and (3) symptoms and signs of raised intracranial pressure – usually the result of hydrocephalus caused by upward expansion of the tumour into the III ventricle. In addition, children with large tumours may already show evidence of a hypothalamic disturbance (usually hypothalamic obesity) at the time of their presentation.

The aims of treatment can therefore be described as reversing – or at least preventing the progression of – symptoms in any of these categories, as well as the prevention of recurrence (cure) of the tumour while leaving the child in an acceptable functional state physically, ophthalmologically, hormonally and behaviourally.

The situation today

The treatments most frequently employed in the treatment of craniopharyngioma today can be summarised as (1) *surgery* – which can vary in scale from an attempted complete (radical) removal, through elective subtotal removals to cyst punctures that can be carried out either stereotactically or endoscopically – and, (2) *radiotherapy* – usually given as a course of external fractionated treatments.

The two extremes of management are best exemplified by the series presented by Yasargil et al. [12], who describes the results of treating 70 children by radical surgery (with an overall mortality of 20% and a "good" clinical outcome in 60%) and that of Brada and his colleagues [10], who describe their experience of treating 77 children aged between 3 and 16 years who were referred for radiotherapy following only limited surgery (progression-free survival rate of 83% at 10 years and "excellent" functional results, 52% of their overall survivors being in their grade 1). It should be noted, however, that neither of these papers (both of which deal with both adult and paediatric cases) describe the functional status of their surviving children in specific detail.

It was against the background of a bad outcome in four children who had presented to our unit as acute emergencies with large craniopharyngiomas that we set out to determine whether it was possible to predict the outcome following radical – or attempted curative – surgery from our own experience.

The first findings to emerge from our retrospective study (which included the four children mentioned above) allowed us to quantify the connection between hypothalamic damage (as demonstrated on MR scanning) and clinical evidence of hypothalamic dysfunction – in this case obesity as measured by the body mass index (BMI). The analysis of three-dimensional, volume-acquisition MR scans reconstructed in the sagittal plane confirmed that with increasing severity of hypothalamic damage the child's BMI also rose – it was five times the normal value in those children with the most damage [3].

The second part of the study [5] looked at prognosis with regard to both morbidity and tumour recurrence. For the former we devised a morbidity score incorporating a variety of neurological, psychological, ophthalmological and endocrinological measures. These were set against details of the child's presentation and their surgery (including any per-operative complications) and the results of their neuro-imaging.

Factors predicting the outcome (morbidity) at the time of the assessment (the actuarial survival period of the 75 patients in our study, 29 of whom were under 5 years of age at diagnosis, was 8.5 years) were the grade of hydrocephalus if present ($P>0.00001$), the occurrence of any per-operative complications ($P>0.02$) and age under 5 years at presentation ($P>0.02$).

The presence of symptoms and signs of hypothalamic dysfunction at the time of diagnosis also had a significant effect upon the immediate post-operative morbidity score ($P>0.01$), but when hypothalamic dysfunction was assessed on its own it was found to have a highly significant effect upon both the immediate post-surgery and the time-of-study assessments.

From our data we concluded that younger children presenting as an emergency (usually with hydrocephalus and thus with the larger tumours) were likely to do badly following an attempt at a complete removal (which was the initial treatment policy in 58 of our patients). This raised the question of whether the pathological anatomy of a craniopharyngioma varies with the patient's age – is the "older" hypothalamus more resistant to surgical trauma? – the clinical picture of severe hypothalamic damage (as described above) being seen less commonly in adults.

Our study also demonstrated the relative risks of tumour recurrence and showed that they could be correlated with the child's age at presentation (<5 years, $P>0.03$), tumour size (as measured by the number of intracranial compartments involved by the tumour, $P>0.00001$), the "apparent completeness" of the surgical excision ($P>0.00001$) and the use of post-operative radiotherapy ($P>0.004$), confirming that post-operative conventional (external fractionated) radiotherapy remains an invaluable part of the treatment of these difficult tumours. Unfortunately, because of the deleterious effects of radiotherapy upon the developing brain (and in particular the hypothalamic/pituitary axis) it is our policy not to employ it at all for children below the age of 3 years, and to postpone it for as long as possible even after that.

The future

What has been described so far might be summarised as the current management of childhood craniopharyngioma and its problems.

From our own experience, we can be reasonably sure of three facts: that radical surgery, while capable of providing long-term tumour control, can in certain (and predictable) cases be responsible for an unacceptable degree of hypothalamic damage; that external fractionated radiotherapy damages the developing brain but may, like radical surgery, provide long-term tumour control; and that younger children fare worse than older children.

What has been learned from our own studies and the experience of others that might help us in the future to achieve the ultimate goal of decompressing the visual apparatus and preventing further tumour growth, while at the same time preserving not only hypothalamic function but also, if possible, pituitary function?

New surgical strategies

Staged surgery

We have observed that the technical difficulty of an attempted complete removal of a large craniopharyngioma can be reduced if any large cystic component is dealt with (using some form of stereotactically guided aspiration) before direct tumour surgery is attempted. The decompression achieved in this way may also be sufficient to relieve any hydrocephalus that may be present by reducing upward compression upon the III ventricle.

Even a solid tumour that extends from the sella to the III ventricle can be dealt with in stages: if the lower part of the tumour is removed first then a subsequent MR may reveal descent of the upper portion of the tumour into a more accessible position. We have also treated a large craniopharyngioma that extended up into one lateral ventricle by separate craniotomies carried out at the same session, as suggested by Yasargil et al. [12], leaving that portion within the hypothalamus to be treated with radiotherapy.

Staged surgical procedures, none of which is intended to achieve a complete tumour removal, may also make it possible to "buy time" until a child is old enough either to be treated with external fractionated radiotherapy or (and this is conjecture), if radiotherapy has already been given, until a radical operation aimed at complete removal may have a less destructive effect upon the hypothalamus.

New anatomical approaches

Professor Madjid Samii of Hanover has observed that as craniopharyngiomas arise as midline tumours, regardless of where they may later extend, the "root" of the tumour will always be in the midline. He recommends therefore a midline – or interhemispheric – approach, and we find that we are employing this not only for recurrent tumours (which was where we first started using it) but also as a first-line procedure.

Cyst instillations

Two methods of treating craniopharyngioma cysts by instillation are presently being tested. These include radioisotopes (the β-emitter yttrium, for example) which may requires only a single instillation, and the chemotherapeutic agent bleomycin, which requires a series of instillations and is said not only to prevent re-accumulation of the cyst but also to produce a thickening of its wall that might make it easier to remove at a subsequent operation.

It should be pointed out, however, that these forms of treatment (which may spare both hypothalamic and pituitary function) will result in a cure only if the tumour is entirely cystic – a type that is not only comparatively rare but also the one most likely to be cured (with an acceptably low hypothalamic morbidity) by radical surgery. Any solid component (being beyond the range of either yttrium or bleomycin) will not be treated and will therefore still need to be dealt with either by surgery or external radiotherapy, if the patient is not to be deemed incurable.

Radiotherapy

There appears still to be reluctance on the part of some neurosurgeons to acknowledge the role of radiotherapy in the management of childhood craniopharyngioma. Although our own study did not look specifically at the effects of radiotherapy (except as one amongst a group of predictive factors for recurrence), analysis of the data suggests that a measure of long-term control was achieved in approximately two-thirds of the patients in whom it was used either electively following a removal that was recognised at the time of surgery as being incomplete or when a tumour previously thought to have been completely removed had recurred. This of course raises the question of what determines the radiosensitivity of individual tumours. Is it related to the relative rarity of the squamous type of craniopharyngioma (as opposed to the adamantinomatous) in younger children or to other factors? (See [1] and [11] for opposing views on the importance of pathology upon the presentation and outcome of craniopharyngiomas.)

The recent introduction of systems to improve the focus of "conventional" external fractionated radiotherapy using relocatable stereotactic frames promises a significant reduction of the dose received by the temporal and frontal lobes – work that has been pioneered by Dr. Nancy Tarbell in Boston [6]. It should also not be forgotten that surgery, in the form of both elective subtotal removals and cyst aspirations, has a role in reducing the target size for subsequent radiotherapy.

The role of radiosurgery remains controversial. The close proximity of the hypothalamus and the optic chiasm means that even with the most accurate planning they are in danger of receiving an unacceptable dose during the single treatment session. Our only experience to date has been with a small intrasellar recurrence in a child aged 2 years who was already blind at the time of his original presentation and who was successfully treated using a Linnac system.

Use of an algorithm

Over the last few years we have developed an algorithm for the management of childhood craniopharyngioma (Fig. 1). This should not be taken as definitive therapeutic advice about what is one of the most difficult tumours in paediatric neurosurgery to treat satisfactorily, but as an example of how knowledge of the factors that determine the outcome with regard to both tumour recurrence and the functional condition of the child can be used to place treatment on a more rational basis.

Concentration of cases

The rarity of childhood craniopharyngiomas makes it difficult not only for a single neurosurgical unit to accumulate experience but also for the paediatric endocrinologists, ophthalmologists and radiation (and medical) oncologists whose input is essential for their care to do the same, and then for all these specialties to share their experience in a useful way.

This is not a problem that can be overcome merely by pooling data from multiple centres; the differences between patients and their tumours and also in the various treatments deployed are too great to allow for any meaningful conclusions to be drawn. Only the concentration of cases into a small number of paediatric centres in which the complete team of experts can be deployed offers any opportunity for improving their outlook.

Conclusions

Rather than summarise the points I have raised about the management of childhood craniopharyngioma, I would like instead to list a series of questions (some of which I

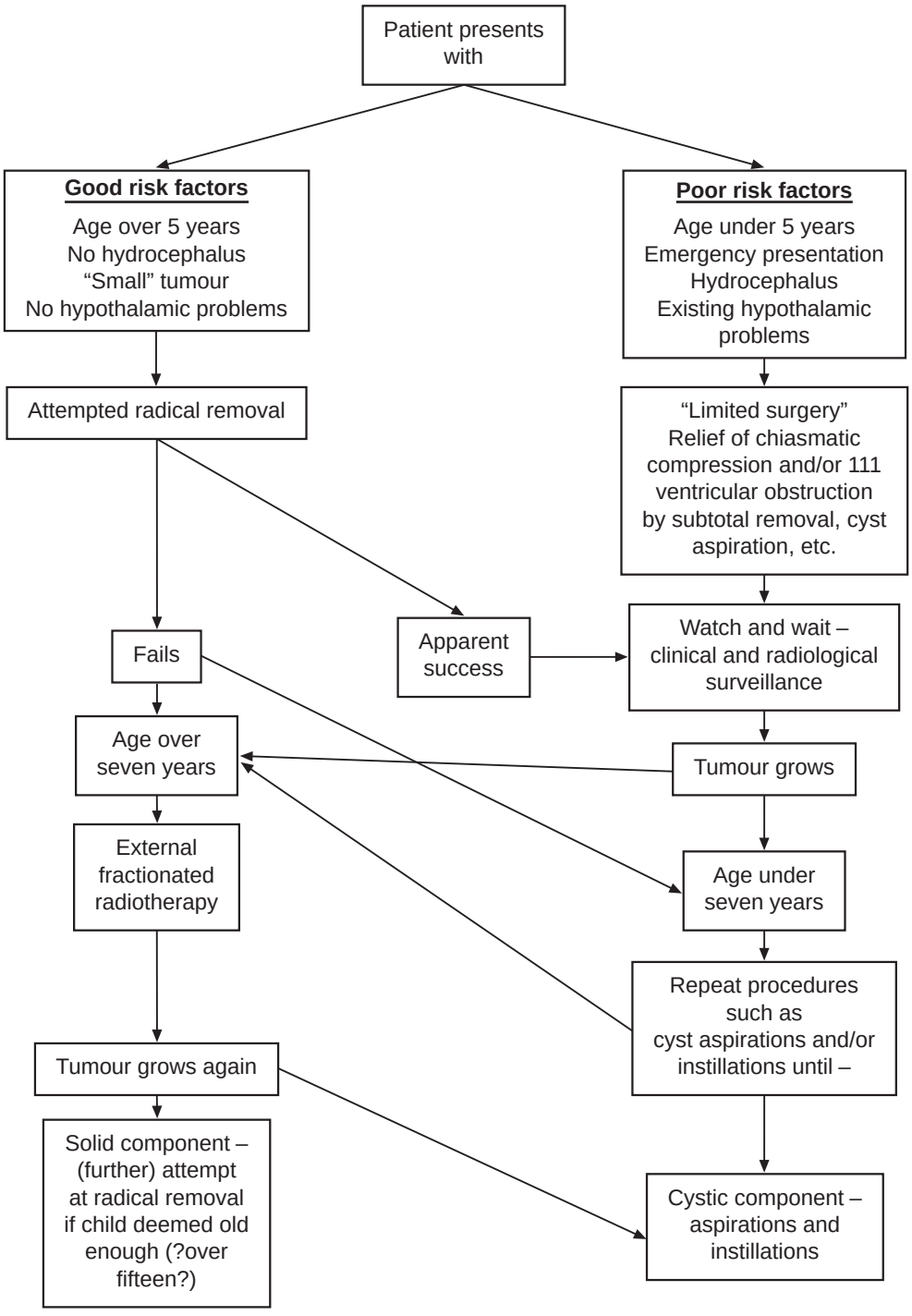

Fig. 1 An algorithm for the management of childhood craniopharyngioma

have already attempted to deal with) whose answers would further increase our knowledge of the behaviour of these difficult tumours and thus – hopefully – improve the outlook for the children presenting with them in the future.

1. Should we, as paediatric neurosurgeons, acknowledge that some childhood craniopharyngiomas are surgically incurable if an unacceptable disability in terms of hypothalamic damage is to be avoided?

2. Can such tumours be identified before surgical treatment is instituted?

3. Does the morbidity of radical surgery fall as a child gets older?

4. Can the response of an individual tumour to radiotherapy be predicted?

5. Will the use of stereotactically focused external fractionated radiotherapy allow us to reduce the age at which such treatment can be employed without increasing the risk of damaging a child's cognitive functions?

6. Is there a role for radiosurgery?

7. What is the role of intra-cyst instillations of yttrium or bleomycin?

8. Given the sophistication of modern imaging techniques, how long should radiological follow-up be continued before a child can be considered cured?

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