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EDITORIAL

Osteoporosis in neurological disorders

Osteoporosis is defined as "low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and consequent increase in fracture risk."[1] It is a major public health concern, with 50 000 hip and an estimated 50 000 vertebral osteoporosis related fractures occurring annually in the United Kingdom, with an annual cost of more than £500 million.[2] Until recently the condition was widely seen as an inevitable and untreatable consequence of aging. However, the introduction of dual energy *x* ray absorptiometry (DXA) scanning as an investigative tool, and the emergence of effective treatments have led to an explosion of clinical, academic, and commercial interest in the field. This editorial reviews its relevance within neurology and presents recent guidelines for the management of steroid induced osteoporosis.

Overview

To date there have been no prospective case-control studies of fracture risk in neurological conditions. However, there are good reasons why some neurological patients may be at particular risk of osteoporosis and fracture. Although the aetiology of osteoporosis is multifactorial (with genetic factors accounting for 70% of the variability in bone density) exposure to high dose corticosteroids and poor mobility are two important potential causes. In addition, epileptics are a separate group at particular risk of fracture.

Bone physiology

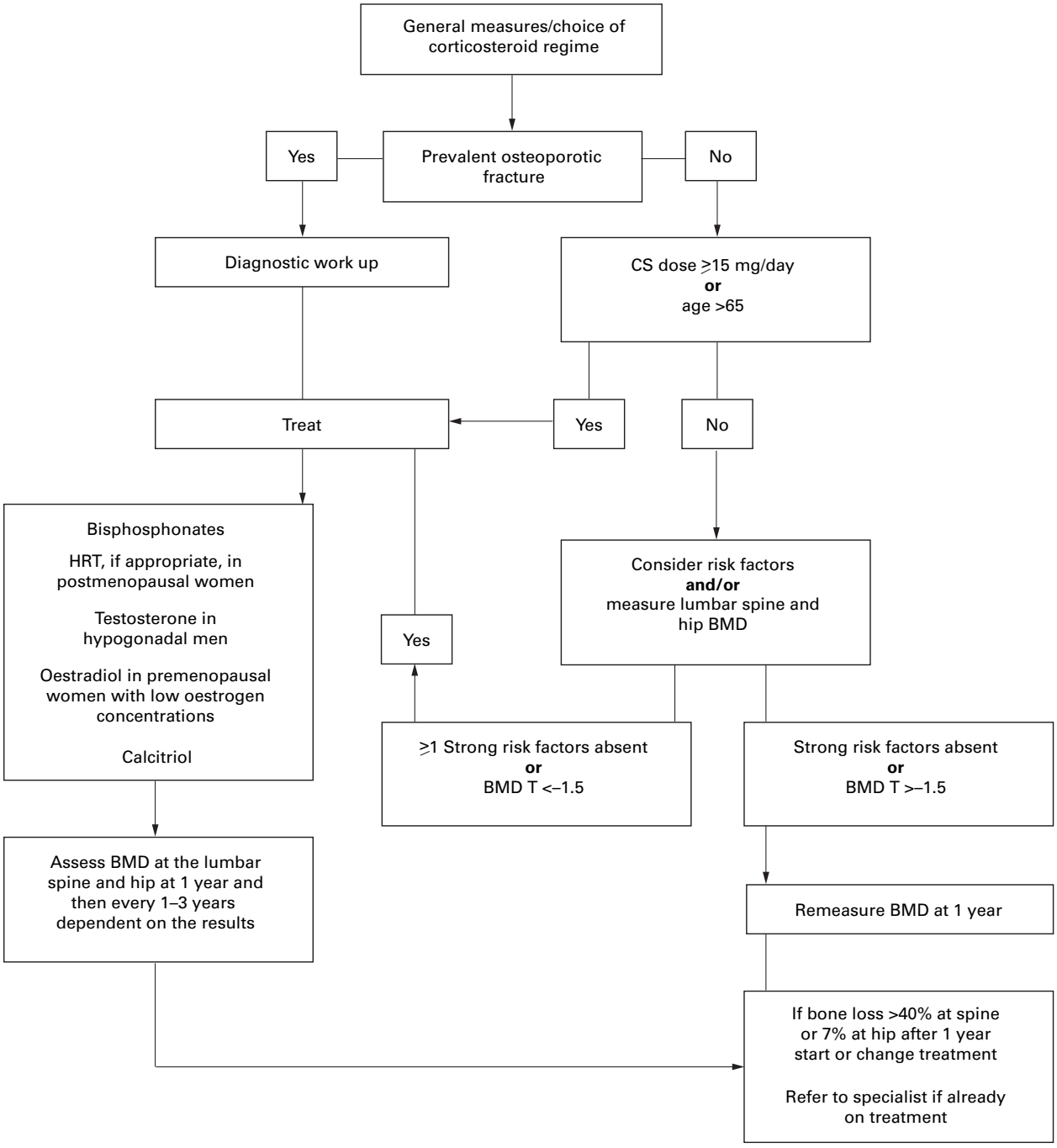
Some knowledge of bone physiology is useful in the understanding of osteoporosis and its treatment. To adapt to stress and to maintain calcium homeostasis bone undergoes a constant process of remodelling. In this process "remodelling units", of which around a million are active at any one time within the skeleton, remove and replace bone in a coordinated manner via osteoclasts and osteoblasts. Net bone loss occurs when there is increased osteoclastic activity or decreased osteoblastic activity. In normal subjects bone density declines slowly from around the age of 30 years at a rate of roughly 1% a year due to a combination of these factors. Most osteoporotic treatments act by reducing osteoclastic activity.

Making the diagnosis

At present DXA scanning is the best and most widely used tool for assessing osteoporosis and fracture risk. The method uses high and low energy x ray beams to measure bone and soft tissue attenuation. A bone density based on an areal density, and expressed as g/cm^2, is computed. Results from DXA are also expressed as SD, either from the mean of an age matched female population (Z score) or from a young population with peak bone mass (T score). There is debate as to which scale is the most clinically relevant. The T score is used by the World Health Organization (WHO) to give definitions of osteoporosis based on DXA readings, and is used in the algorithm accompanying this editorial. Thus, a T score of more than 2.5 SD below the peak bone mass is considered by the WHO to represent osteoporosis and between 1 and 2.5 SD below the mean represents osteopenia.[3] Because bone density declines with age, most of the very old will therefore have bone densities within an osteoporotic range. In general, the risk of fracture increases twofold to threefold for each SD decrease in bone density. A T score of –2.5 is said to be the "fracture threshold"; below this level, 90% of fractures will occur. There is some evidence that in patients treated with steroids, the fracture threshold may be higher.[4] Scanning with DXA is quick, cheap, and safe, with less than 5 mRem radiation exposure (a chest radiograph involves 20–30 mRem). Falsely high readings can be obtained secondary to vertebral fracture and osteoarthritis.There are no known causes for a falsely low reading. The precision of the technique is good, around 1-2%, but the rate of change of bone density in most situations is relatively slow, and repeat scans to assess response to treatment are only accurate after 3 years. Department of Health guidelines now suggest DXA scanning may be considered in those at risk of secondary osteoporosis, including those taking more than 7.5 mg prednisolone daily for more than 3 months (figure).[5]

The role of corticosteroids

Corticosteroids have the potential to induce bone loss via several mechanisms, including reduced intestinal calcium absorption, increased urinary calcium excretion, reduced osteoblast function, and inhibition of sex hormones.[6] The relative contribution of each of these mechanisms is not clear. The precise risk of osteoporosis and fracture is also difficult to assess, most studies having been cross sectional rather than longitudinal. Fracture rates as high as 50% have been described in corticosteroid treated asthmatic patients[7] and early work on rheumatoid arthritis suggested that steroid doses as low as 10 mg daily caused marked early loss of bone, with incomplete recovery as the dose was tapered.[8] A recent systematic review of 23 prospective studies of corticosteroid treatment suggested that patients with rheumatoid arthritis lost no bone density at the spine, but 3% at the hip/year. Eleven of the studies looked at non-rheumatoid arthritis patients; the relevant figures here were 4.7% loss at the spine and 1.5% at the hip. Only one of these studies included patients with neurological



The prevention and management of corticosteroid induced osteoporosis. An algorithm to apply to any adult patient about to commence or currently being prescribed an oral dose of 7.5 mg/day or more of prednisolone or equivalent dose of another corticosteroid for 6 months or more. Algorithm taken from "Guidance on the prevention and management of corticosteroid induced osteoporosis" with permission of the National Osteoporosis Society.

disease.[9] More recent work has suggested that effects of corticosteroids are influenced by the background condition for which they are used. Although corticosteroids seem to lead to some early bone loss, particularly in the trabecular bone of the spine (where bone turnover is more rapid), this can be at least partly offset by beneficial effects in reducing inflammation and improving mobility.[10 11] The importance of functional ability extends to fracture risk, with a case control study of hip fracture in rheumatoid arthritis showing that fracture risk was mainly attributable to functional status.[12]

This balance between steroid dose and functional ability seems to exist in neurological conditions. A retrospective study of 103 consecutive attenders at a multiple sclerosis clinic found that 25% had fractured, at an average age of 38 years. High dose steroid treatment did not seem to clearly increase fracture risk.[13] Reduced bone densities at the spine and hip (mean Z scores –0.98 and –1.72 respectively), unrelated to steroid dose, were found in 80% of female patients with multiple sclerosis. In this study a high prevalence of low vitamin D concentrations, possibly secondary to poor dietary intake and low exposure to sunlight, was also found.[14] A more recent prospective study looking at 30 patients with multiple sclerosis given 3 g methylprednisolone and a 2 week course of oral prednisolone found that femoral bone density improved slightly over 6 months in those patients whose mobility improved, but fell in poorly ambulatory subjects. At baseline density of the

femoral neck bone was mildly reduced (Z score −0.87) but lumbar spine bone density was normal. Again, there was no correlation with prior steroid treatment.[15] There have been no reports of bone density in myasthenic or myositic patients, although in a preliminary analysis of steroid treated myasthenic patients seen in our unit we found minor degrees of bone loss in over 50% of patients.[16] The hip seemed to be more affected than the spine or forearm, which is in accord with other studies looking at poorly ambulatory patients with multiple sclerosis.

Spinal cord injury and the role of immobility

Acute spinal cord injury leading to paraplegia leads to a rapid increase in bone resorption. The effect is due to both early increased resorption and later diminished formation.[17] Studies in these patients also show a consistent trend for hip bone density to be lower than the spine,[18–20] suggesting that weight bearing stress is important in maintaining bone density. A large cross sectional study of 176 paraplegic and tetraplegic patients showed hip bone density to be reduced by 20% compared with controls. The reduction was seen after 1 year of illness, although there was little difference between the groups who had been paralysed for 1–9 years or 10–19 years, suggesting that a steady state of resorption/formation may develop. Surprisingly, spine bone density was normal in paraplegic and tetraplegic patients.[18] By contrast, a prospective study following up 31 patients for 1 year after spinal cord injury found a 4%/month loss of trabecular bone mineral content in paralysed areas.[21] It does not seem that spasticity in paralysis protects against bone loss.[19 21] There also seem to be some bone abnormalities particular to paraplegic patients, with marked loss of proximal tibial bone density[20] and a high risk of distal femur supracondylar fractures.[22] The cause of these changes is not clear; although some explanations, including disordered vasoregulation, have been suggested. Data on fracture incidence in patients with spinal cord injury are scant. However, as many as three quarters of patients may have fractures at some stage.[18] A study of 277 polio patients in Olmsted County showed an increased risk of distal femoral and proximal humeral fractures, which seemed to be related to the site of paralysis.[23] The mechanisms by which immobility leads to bone loss and by which skeletal loading leads to an alteration in bone mass and distribution are unclear. However, cross sectional and longitudinal studies in athletes have shown that weight bearing exercise (in particular, high impact loading) has a more profound effect in increasing bone density than even intense non-weight bearing exercise.[24–26] The topic has recently been extensively reviewed.[27]

Epilepsy

Epileptic patients are another group at increased risk of fracture. Both phenytoin and phenobarbital increase the metabolism and clearance of vitamin D and have been associated with frank osteomalacia, particularly in institutionalised patients.[28 29] Carbamazepine has also been implicated as a cause of osteomalacia.[30] A further study of an institutionalised epileptic population found a high incidence of femoral fractures (nine times greater than a control population for intertrochanteric fractures) as well as an increased risk of wrist, ankle, and humeral fractures. Only 25% of the fractures were related to fits and the increased risk was spread evenly throughout the age groups.[31] Studies of rib and vertebral fractures are lacking in epileptic patients, although the clinical impression is that these are often related to fits. The high rate of fracture in institutionalised epileptic patients suggests that some form of prophylaxis, including calcium and vitamin D, should be considered.

Falls

Most fractures occur as the result of falls. These are more common with increasing age and a recent study of nursing home residents showed that each resident had an average of 1.4 falls over 3 years.[32] In elderly people up to 5% of these falls may lead to fracture.[33] In comparison, a study in a neurorehablitation unit (commonest conditions: spinal cord injury, brain injury, and multiple sclerosis) showed that each patient had an average of 1.4 falls a year.[34] A large study of women over 65 years old showed that some risk factors increased the risk of hip fracture independent of bone density. Presumably these factors act by increasing falls or by adversely affecting an element of bone strength not measurable by bone densitometry. Some would seem to apply to patients in the later stages of some neurological conditions, including inability to rise from a chair, poor depth perception, and the use of long acting benzodiazepines. In epileptic patients, those taking anticonvulsant drugs were found to have a twofold risk of hip fracture, again independent of bone density. No fractures occurred during a fit.[35]

Treatment and prevention

Steroid induced osteoporosis has now become a medicolegal issue which makes it difficult for clinicians to ignore.[6] A consensus group has recently set a prednisolone dose of 7.5 mg daily or more for 6 months or more as the level at which patients treated with steroids should be considered (see figure). The algorithm was developed to help clinicians in different situations (who may not have access to DXA services or specialists in osteoporosis) cope with the many patients given corticosteroids. From the algorithm, some patient groups, including those over 65 (who will already have a high prevalence of osteoporosis) or those starting on doses of 15 mg or more, should be given preventive treatment at the start of steroid treatment without waiting for referral or specialist advice, as further investigation is unlikely to alter management. Difficult cases, such as children, should still be referred to a specialist. The agents suggested in this algorithm have been shown to reduce risk of fracture in non-steroid treated patients. So far, because of low patient numbers and short trial durations, data in steroid treated patients have shown only an effect on bone density.[36–39] Patients with neurological conditions have been poorly represented in these trials. For example, the largest prospective study so far in the prevention of corticosteroid induced osteoporosis (477 patients), which used alendronate, included only three myasthenic patients in the treatment arms.[39] A small histomorphometric study of the bisphosphonate tiludronate in paraplegic patients did show a beneficial effect at a dose of 400 mg daily.[40] In those neurological patients with swallowing difficulties, the intravenous bisphosphonate pamidronate, given at 3 monthly intervals, may be a useful alternative. Based on observational data and the trials available, the consensus group graded the expected effectiveness of interventions; bisphosphonates are at present thought to be the most effective, although there are also likely to be benefits from vitamin D, hormone replacement, and glucocorticoid analogues. Bisphosphonates available in the United Kingdom include etidronate, alendronate, pamidronate, and tiludronic acid and clodronate. Of these, only etidronate (as Didronel PMO) and alendronate are licenced for use in osteoporosis, and only Didronel PMO for use in steroid induced osteoporosis. The most widely used glucocorticoid analogue is deflazacort, an oxazoline analogue of prednisolone. This may have less effect on bone metabolism and fewer systemic effects than prednisolone for an equivalent anti-inflammatory effect. However, the data are

based on small numbers and even on deflazacort, bone loss continues.[41] However, for children or patients on high doses with metabolic side effects or fracture, this is a useful alternative drug.

Despite the common use of alternate day steroid therapy in neurological conditions, there is no evidence that this regime has bone sparing benefits in adults over equivalent daily dosing.[6] However, the studies have been performed in asthma and rheumatoid arthritis and there are to date no studies in neurological conditions.

In patients not treated with steroids physicians may refer to Department of Health guidelines on the management of osteoporosis. These identify hormone replacement therapy, tibolone, bisphosphonates, calcitriol, calcium and vitamin D, and calcitonin as treatment agents, without attempting to grade efficacy.[5] A recent review of postmenopausal osteoporosis examined fracture data for all commonly used agents and suggested that HRT remains the treatment of first choice,[42] although much of the evidence for this agent is observational. Most commonly used agents lead to roughly 50% reduction in fracture rate, probably because all work in a similar way in reducing bone resorption.[43]

Non-pharmacological approaches

Fracture risk depends on other variables apart from bone density. These include fall risk, hip geometry, bone quality and, possibly, amount of trochanteric fat. Non-pharmaceutical interventions have been shown to reduce the risk of falls and fracture in elderly people. These include balance training[44] and the wearing of hip protectors. The second have been shown to reduce fracture rates by half.[45] The beneficial effects of weight bearing exercise have also been shown in normal subjects.[46] In patients with spinal cord injury electrically stimulated leg cycling has shown minimal benefit in improving spine bone density[47]; a similar ambulatory system showed no benefit.[48]

The future

Osteoporosis remains a field of intense research activity which touches on many fields of medicine. Unexpected risk factors, such as the immune modulators tacrolimus and cyclosporin, have been recently described[49] and in diagnostics the use of peripheral DXA screening and ultrasound are being explored. The selective estrogen modulators (SERMS), including raloxifene, have recently been launched which show promise in having a positive effect on cardiovascular as well as skeletal sites.[50] New treatments being investigated include bone stimulating agents, such as parathyroid hormone, which have the potential to increase bone density in excess of the antiresorptive agents.

Conclusion

Osteoporosis is likely to become an increasingly important issue in neurology. Simple guidelines are now available for drug treatment and prevention of glucocorticoid induced osteoporosis and all patients on moderate doses of steroids (more than 7.5 mg for more than 6 months) should be treated or referred for a specialist advice. For non-steroid treated patients at particular risk of osteoporosis and fracture, including epileptic patients and those with poor mobility, no similar guidelines yet exist. However, a reasonable approach would be to perform bone densitometry in individual cases and follow the same treatment algorithm. In epileptic patients osteomalacia (which may be difficult to distinguish from, and may coexist with osteoporosis) should be considered. Other non-pharmaceutical measures to prevent falls and their consequences should be employed when possible. In all patients the importance of maintaining functional status, and weight bearing, although obvious, cannot be overemphasised.

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EDITORIAL COMMENTARY

Clinical evaluation of patients with stroke is still worthwhile

Do we still need clinical evaluation in the era of "high tech" functional neuroimaging, or should we just rely on machines? For those of us who care for patients with stroke where they are normally admitted—that is, peripheral hospitals with poor access to complex facilities—the answer is obviously yes, and the results shown in the paper by the Edinburgh group (this issue, pp 558-562)[1] are an important confirmation of this view.

After CT to rule out a haemorrhage, the clinical distinction between total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), posterior circulation infarct (POCI), and lacunar infarct (LACI), as defined in the Oxfordshire Community Stroke Project (OCSP) study,[2] which is based on history and examination, gives important information to the clinician. In fact, not only the site and size of the future infarct on CT can be reasonably predicted (a fact which is scientifically important, but has no practical value for the actual management of the patient), but also solid hints on the pathogenesis of the ischaemia can be made, and therefore a diagnostic programme can be established more reliably, especially when the access to additional investigations is not easy. The authors[1] correctly point out that if the patient has been labelled as having had a LACI, the probability of finding important and surgically treatable lesions on carotid Doppler or transoesophageal echocardiography is low. However, these tools have a very important role in patients with PACI, where an embolic source is very likely, and a better and more rational use of resources can be made using this classification.

Some clinicians involved in stroke research think that there is little or no value in the OCSP classification, in the very acute phase of the stroke; in fact, Mead and colleagues rightly point out that a formal validation of the OCSP classification in the hyperacute phase of the stroke, when symptoms and signs may change within a few hours, would be useful. However, some work in this direction has already been made, using data from the International stroke trial,[3] and looking at the prediction of outcome (which is clinically meaningful) instead of the future presence of a lesion on a repeated scan; results show that even for patients evaluated within 6 hours the OCSP classification still correctly predicts the short term outcome of the patient,[4] and can be used to stratify patients very early, when a CT is usually normal.

Stroke doctors are not yet (and will probably never be) in the position of Dr Leonard "Bones" McCoy, the physician of the Enterprise starship in Star Trek movie, who could make any possible diagnosis by means of a very sophisticated machine, without talking to the patients or even touching them; we have still to rely on our clinical skills to direct the diagnostic itinerary and, possibly, the therapeutic decisions. Therefore, while waiting for further research on this topic, we can apply the OCSP classification in our clinical setting, and recommend its wide use in epidemiological research and in clinical trials, to make results really transferable to clinical practice.

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EDITORIAL COMMENTARY

How effective is radiosurgery for arteriovenous malformations?

Complete surgical excision is the treatment of choice for accessible arteriovenous malformations (AVMs). Non-invasive alternatives of radiosurgery and embolisation are generally offered to patients with inaccessible AVMs with the hope of equivalent effectiveness and low morbidity. Kurita *et al* in this volume (pp 563–570)[1] advocate radiosurgery as a "viable" treatment modality for brainstem AVMs which is "safe and effective" for small lesions. Do we really have a cure for previously untreatable AVMs? Let us examine the evidence for the risks and benefits of this treatment technique.

Radiosurgery refers to single high dose localised irradiation, given using either a gamma unit (gamma knife, multiheaded cobalt unit) or a linear accelerator (linac radiosurgery, X-knife radiosurgery). It aims to destroy blood vessels of the AVM nidus, while avoiding injury to normal brain and this is achieved by focusing radiation onto the lesion. The effectiveness of radiosurgery is generally measured in terms of disappearance of abnormal blood vessels on angiography. After radiosurgery, the rate of angiographic obliteration increases with time and is size and radiation dose dependent. The reported obliteration rates at 2 years are in the region of 80% to 90% for small lesions (<2 cm diameter) and 40% to 60% for larger lesions. There is however, some concern about the reliability of the figures if angiographic follow up is incomplete.[2] By analogy with surgical treatment, where absence of an angiographically visible AVM represents removal of abnormal vessels and therefore no further risk of bleeding, it is assumed that no visible AVM after radiosurgery means no risk of bleeding. This analogy may not be appropriate as the mechanism of radiation induced blood vessel obliteration is occlusion of vessels, which remain in situ. Obliterated AVMs, such as seen after embolisation, have been known to recanalise and may be at risk of bleeding. Angiographic obliteration is therefore not a sufficiently rigorous end point to assess the efficacy of radiosurgery.

Untreated AVMs have a tendency to bleed with consequent morbidity and mortality. The principal aim of treatment should therefore be improvement in survival, quality of life, and neurological progression free survival. As there is scant information on these variables after radiosurgery, we have to rely on an intermediate end point of rebleeding. Although of importance it does not include potential treatment related morbidity and mortality.

In the first 2 years after radiosurgery there is an increased risk of haemorrhage with a reported annual risk of rebleeding ranging from 4% to 8%.[3–5] This compares with the natural history of a 2% to 4% annual rebleeding rate of untreated AVMs. It is claimed that after complete obliteration, there is no further risk of bleeding, although there is not sufficient statistically reliable long term data to prove this point and there are occasional case reports of late haemorrhage.[6 7] Rebleeding is reported in patients who do not achieve complete obliteration after radiosurgery[8] but the overall risk of rebleeding for the whole treated or "intent to treat" population is not defined.

Radiosurgery is not without complications as the aim of high dose irradiation is to cause late normal tissue damage to the blood vessels. Although the term radiosurgery might invoke highly localised therapy and damage confined to the target, the physical principles of radiation mean that surrounding normal brain always receives some irradiation. The volume of normal brain irradiated by high doses and therefore the risk of injury increase with the size of the lesion and the radiosurgery dose. The AVMs are often embedded in normal functioning brain, which is also responsible for treatment toxicity as it receives the full radiosurgery dose. The reported actuarial risk of damage 2 years after radiosurgery, detected as areas of high signal intensity on T2 weighted MRI, is around 30% and most damage spontaneously resolves.[9 10] The reported actuarial risk of symptomatic damage at 2 years is about 10%, of which half the patients improve.[9 10] The overall risk of symptomatic toxicity depends on radiosurgery dose, the volume of brain irradiated to high dose and the eloquence of the treated site.[11] The predicted risk of symptomatic toxicity is in the region of 5% for 2 cm diameter volume and 10% for 3 cm diameter volume receiving $\geq$12 Gy. For brainstem lesions the predicted risk of symptomatic toxicity for equivalent volumes receiving $\geq$12 Gy is 10% and 30%.[9] The usual marginal dose to AVM is 17–20 Gy and the predicted risk would be marginally higher. Balancing the risks and benefits the therapeutic ratio is generally in favour of radiosurgery for small lesions in non-eloquent areas treated with high doses but the answer is not entirely clear for large AVMs and for treatment of eloquent areas.

In this context how effective is radiosurgery for brainstem AVMs? Kurita *et al*[1] judiciously chose small brainstem AVMs with a mean diameter of 1.3 cm (range 0.6–2 cm) and provide excellent long term follow up data. The incidence of radiation induced injury, after an appropriately modest radiosurgery dose, was in the region predicted by modelling, with little permanent radiation injury, contrary to other reported experience.[12] Nevertheless, the results are disappointing. In the first 2 years after radiosurgery, there was an apparently increased risk of rebleeding with an annual rebleeding rate of 6%. On subsequent follow up, for up to 8 years, the annual bleeding rate was 2.7% (and 1.9% for patients receiving higher radiosurgery doses), with a 5 year actuarial haemorrhage free survival of 81% and a 5 year survival of 88%. Within the reported follow up, radiosurgery with generally accepted doses, is therefore not particularly effective for patients with brainstem AVMs. Improving the efficacy of radiosurgery at this site would mean higher radiosurgery dose with greater risk of radiation injury; it may well be that in eloquent regions such as the brainstem the therapeutic ratio cannot be improved.

Radiosurgery, with its marketing appeal, seems an attractive non-invasive treatment option for small AVMs, which results in high obliteration rate at a modest toxicity. However, angiographic obliteration alone is not a sufficient end point to balance the risks and benefits of different treatment approaches. As illustrated in the report of brainstem AVMs, only long term survival, quality of life/neurological progression free survival, and rebleeding rate are likely to

provide objective comparative data on the effectiveness of all treatment strategies including radiosurgery.

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