which is important—whether or not it can be measured accurately.

DIANA BRINKLEY

Consultant Radiotherapist,
South East London Radiotherapy Centre,
King's College Hospital,
London SE5 9RS

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Cranial irradiation in childhood lymphoblastic leukaemia: time for reappraisal?

Fifteen years ago the first Medical Research Council United Kingdom acute lymphoblastic leukaemia trial introduced Britain to the concept of treatment to prevent overt leukaemic infiltration of the central nervous system, so called "central nervous system prophylaxis."[1] Without such prophylaxis most children who survive lymphoblastic leukaemia go on to develop this complication. Established leukaemia in the central nervous system is difficult to eradicate, causes considerable discomfort, and is associated with a risk of further neurological complications.[2] Thus central nervous system prophylaxis proved a welcome advance and one which, coupled with intensified combination therapy, has led to growing numbers of cures in children with acute lymphoblastic leukaemia.

The method of prophylaxis introduced in the Medical Research Council United Kingdom acute lymphoblastic leukaemia I and II trials—and which had been pioneered in St Jude Children's Research Hospital in Memphis—comprised a course of cranial irradiation in a dose of 2400 rads (cGy), usually given in 15 fractions over three weeks with concomitant intrathecal methotrexate or spinal irradiation or both.[3,4] The combination of cranial irradiation, 2400 rads, and intrathecal methotrexate was widely adopted as standard prophylaxis in Britain and many centres abroad, although some centres have never used cranial irradiation or abandoned it in favour of alternative methods, such as moderate dose intravenous methotrexate with intrathecal methotrexate,[5] or triple intrathecal chemotherapy.[6]

The possibility that cranial irradiation might impair cerebral function has long been considered[7] but has been difficult to prove because of the problems of prospective studies in a disease with a high attrition rate, the need for long term follow up, the young age of the most vulnerable patients, and the compounding social and emotional problems that are encountered in children with acute lymphoblastic leukaemia and their families.[8] Not surprisingly, therefore, many reported studies of intellectual function have been retrospective or based on relatively small numbers of patients, or both.[9-11] Nevertheless, these reports show that children who have received "standard" central nervous system prophylaxis usually function intellectually within the normal range but tend to perform less well than their siblings or social peers. Differences are most appreciable in young children, particularly those under 3 at the time of diagnosis, whose schooling is least likely to have been interrupted by treatment.[12] More extensive assessment of cognitive function shows a wide range of functional defects in areas such as memory and attention, speed of processing information, and auditory learning[13] (L Jannoun, J M Chessells, paper submitted for publication). These deficits are not usually apparent on routine screening or intelligence testing alone. A recent retrospective survey has shown that children whose prophylaxis included cranial irradiation performed significantly less well than those receiving intrathecal methotrexate alone, or intrathecal and intravenous methotrexate.[14] These observations—which obviously implicate cranial irradiation—require confirmation in view of reports where abnormalities in computed tomograms occurred irrespective of whether the child had received cranial irradiation.[15,16] Regrettably, in view of the increasing use of bone marrow transplantation there are no reports of neuropsychological function after total body irradiation.

Cranial irradiation causes abnormalities of hypothalamic pituitary function, especially production of growth hormone. Shalet and his colleagues have systematically evaluated endocrine function in children treated for acute lymphoblastic leukaemia and children with brain tumours.[17-20] They estimate that a minimum dose of 2500-2900 rads given over three weeks, or an equivalent radiobiological dose, is needed to produce clinically overt deficiency of growth hormone,[17] and in a recent paper have shown that in some patients at least the abnormality is due to deficiency of hypothalamic growth hormone releasing factor.[18] Although provocation tests in children receiving standard treatment for acute lymphoblastic leukaemia may disclose abnormalities of growth hormone secretion,[19] any substantial impairment of growth is exceptional.[20] Patients receiving a second course of cranial irradiation, however, are clearly at risk of hypothalamic-pituitary failure and require careful follow up. The main cause of impairment of growth after total body irradiation is gonadal failure, but here again hypothalamic pituitary failure may be a contributory factor.[21]

So what is the place of cranial irradiation in childhood acute lymphoblastic leukaemia? The American Children's Cancer Study Group showed that 1800 rads is as effective as 2400 rads, although not perhaps for children with a high initial leucocyte count,[22] and the Medical Research Council has adopted this lower dose regimen together with a policy of deferred irradiation in children aged under 2 years. Neither group, however, has appreciably decreased the size of individual treatment fractions and it remains to be seen whether this lower total dose of radiation is less damaging. Too few studies of neuropsychological function have been published after alternative forms of central nervous system prophylaxis. The best way to prevent leukaemia of the central nervous system has to be determined and may vary with the age of the patient and the clinical features at presentation. Meanwhile, cranial irradiation and intrathecal methotrexate remain the best established way to prevent this chronic and distressing complication of childhood leukaemia.

JUDITH M CHESSELLS

Consultant Physician,
Department of Haematology and Oncology,
Hospital for Sick Children,
London WC1N 3JH

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Phantom pregnancy

Pseudocyesis is a condition in which a non-pregnant—and non-psychotic—woman firmly believes herself to be pregnant and develops objective signs of pregnancy.[1] Most cases are said to occur between the ages of 20 and 39, though the age range in one series was 5-79,[2] and cases have recently been described in teenagers.[3-5] The most common symptom is amenorrhoea or oligomenorrhoea, usually for nine months.[6] There is also abdominal enlargement, but without effacement of the umbilicus. Breast changes, which occur in 80% of patients,[2] include tenderness and swelling, secretion of milk or colostrum, and areolar pigmentation. Patients often claim to feel fetal movements, usually earlier than in a genuine pregnancy.[1] There may be vomiting, morning nausea, aberrations of appetite, and weight gain, and a case of "toxaemia" has been reported.[6] The diagnosis may be difficult,[7] but nowadays should easily be made with the help of ultrasound.[8] Occasional cases have been described in men,[2 9] but these may be associated with psychosis or organic disease.[9]

Phantom pregnancy was first described by Hippocrates and has since affected all races and strata of society, including British royalty, American slaves, and Chinese coolies.[2] It seems to be becoming rarer,[1 2] partly because increasing diagnostic accuracy means that it is no longer confused with conditions like hyperprolactinaemia, partly because in developed countries there is less pressure on women to become pregnant, and partly because of increasing public knowledge about medical matters. Nevertheless, the incidence is still comparatively high among black people in Africa,[10 11] and in developed countries immigrants may remain at risk.[3-5 12] Patients are usually naive about medical matters,[13] and may have either a strong desire for pregnancy or a fear of conceiving.[14] The condition may be a form of hysterical conversion,[3] or depression may be present.[1 6 14] A "pregnancy" may help a woman cope with distress or loss,[6 15] and an association with child stealing has been reported.[12]

What is the endocrine mechanism of pseudocyesis? In laboratory rats pseudopregnancy may be induced by various means, including genital stimulation,[2 16] and is due to persistence of a corpus luteum in the absence of pregnancy; neurogenic suppression of prolactin inhibitory factor may occur, allowing prolactin to help maintain the corpus luteum.[17] In human pseudocyesis, however, a corpus luteum is often absent[2 17] and the basal plasma prolactin concentration may be normal[18 19] or raised.[5 17] Basal plasma concentrations of follicle stimulating hormone are normal,[5 17-19] while the luteinising hormone value may be normal[17-19] or raised.[5] The pulsatile pattern of luteinising hormone and prolactin secretion is exaggerated,[5] and administration of luteinising hormone releasing hormone and thyrotrophin releasing hormone produces exaggerated responses of luteinising hormone and prolactin respectively.[17-19] In a recent study of five patients in Florida the gonadotrophin concentrations were within the normal range but luteinising hormone was consistently higher than follicle stimulating hormone, while prolactin and progesterone were mildly increased.[13] Apart from the raised progesterone value this pattern is similar to that in polycystic ovary disease.

In some types of amenorrhoea—particularly hyperprolactinaemic amenorrhoea—there are increased concentrations of opioid peptides (endorphins). These inhibit pulsatile release of luteinising hormone,[20] and thus administration of the opioid antagonist naloxone to these women stimulates release of luteinising hormone. Since opioid peptides may influence behaviour as well as hormone concentrations it was suggested that their production might be increased in pseudocyesis; but when naloxone was given to women with pseudocyesis it failed to induce release of luteinising hormone or prolactin.[13] After the patients were told their diagnosis, however, the naloxone response appeared to return to normal. This suggests that pseudocyesis is not associated with increased opioid activity, though possibly there may be a reduction in tonic opioid inhibition.

Treatment usually entails confronting the patient with the diagnosis.[15] Normally when this is done hormone concentrations return to normal quickly, the abdominal distension begins to disappear,[5] and there may even be a rapid drop in weight.[21] Nevertheless, patients may resist the diagnosis,[1 7] and once they realise the truth depressive illness may occur.[7] Recurrence is common,[2 4 14] and close cooperation between gynaecologist and psychiatrist is important.[7] Psychotherapy[2 14 15] and family therapy[4] may be necessary, and appropriate follow up is essential.[14 21]

JAMES OWEN DRIFE

Senior Lecturer in Obstetrics and Gynaecology,
University of Leicester,
Leicester LE2 7LX

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