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Correspondence and Short Communications

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TOPICAL CAPSAICIN IN TREATMENT OF HYPERALGESIA, ALLODYNIA AND DYSESTHETIC PAIN CAUSED BY MALIGNANT TUMOUR INFILTRATION OF THE SKIN

Capsaicin, the spicy constituent of chilli peppers, belongs to a family of compounds, the capsaicinoids or vanilloids, that has been shown to stimulate and desensitize specific subpopulations of sensory receptors. These include the C-polymodal nociceptors, A-delta-mechanoheat receptors (rats), warm receptors of the skin, and enteroreceptors of thin afferent fibres (1). Moderate relief of postherpetic pain has been reported in several recent studies (2, 3) and in postmastectomy pain syndrome (PMPS) (4). In man, application to the skin produces a burning pain sensation and/or hyperalgesia to skin heating and pressure (5) and causes vasodilatation. Repeated application within 24 h leads to diminished effects, with reduced or absent pain and less vasodilatation. After several applications the skin becomes completely insensitive to capsaicin (5). We here present a case report achieving control of hyperalgesia, allodynia and dysesthetic pain due to malignant skin infiltration by topical application of capsaicin.

Case Report. A 40-year-old man, previously treated for a non-seminomatous testicular cancer at the age of twenty-six, developed malignant melanoma located on the upper right part of his back. The lesion was treated by extended excision. Six months later he developed skin metastases. After another 6 months of treatment, where new metastatic manifestations were exercised, he developed lung metastases, multiple left supraclavicular lymph node metastases and multiple skin metastases in the left supra- and infraclavicular region. He was treated with two courses of a combination chemotherapy consisting of cisplatin, vindesine and dacarbazine with no sign of response. As the disease progressed, he developed dysesthetic pain, allodynia and hyperalgesia of the skin overlying the malignant process. He was treated with opiates at increasing doses, with the anticonvulsant carbamazepine, antidepressants, steroids and non-steroidal antiinflammatory drugs with little or no effect on his pain. When clothing came in contract with skin the pain was excruciating. The pain caused him to abstain from having visits from his 2-year-old son as the son was likely to touch and hug him. On the basis of reports on the effect in postherpetic neuralgia, we chose to treat the patient by repeated administration (thrice daily) of 0.025% capsaicin cream. Two days after starting treatment the pain disappeared. The patient was treated for 10 days. The topical application was then stopped but reinstituted a week later since the patient was afraid of getting the pain back. The patient remained pain-free until his death four weeks after start of treatment.

Discussion. In adult mammals capsaicin excites nociceptive C-afferents by a direct membrane action involving the opening of channels permeable to sodium, calcium and other cations (6). Initial topical application of capsaicin to skin causes C-fibre excitation and pain. Repeated application causes nociceptor desensitization and hypalgesia in human skin. Axon reflex flare, an 'effector' action of C-fibres, is also diminished or abolished. Clinical trials in man, notably on postherpetic neuralgia, have shown that topical treatment over weeks can give useful pain relief (2, 3). Watson et al. (4) used capsaicin in the treatment of 14 patients with postmastectomy pain syndrome (PMPS). PMPS that occurs in a minority of women after mastectomy is characterized by the onset of pain immediately or very shortly after the operation. Twelve out of 14 patients, completing treatment with topical 0.025% capsaicin, showed improvement after 4 weeks, and 8 (57%) were judged to have good or excellent responses. Six months after the trial completion 50% of those followed continued to have good pain relief. Capsaicin may have further application in pain relief and in inflammatory disease that have a significant neuro-inflammatory component (6). One such indication of capsaicin may be in the treatment of pain due to malignant tumour infiltration of the skin. Tumour infiltration may cause unbearable pain not responding to opioids, non-steroid antiinflamatory drugs, anticonvulsants or anti-depressants. The pain may leave the patient incapable of enjoying normal social relations. In such circumstances capsaicin cream could be tried. Repeated applications of the drug may, as this case history shows, lead to prolonged pain relief. One has to be aware of the fact that capsaicin may induce a transient period of increased pain after the first application even if this was not observed in our patient.

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BILATERAL TEMPORAL LOBECTOMY FOR NECROSIS INDUCED BY RADIOTHERAPY FOR NASOPHARYNGEAL CARCINOMA

Experimental bitemporal lobectomy in adult rhesus monkeys results in Kluver-Bucy syndrome (1). Extrapolating a syndrome from primates to humans may be controversial but the possible consequence is so distressing that bilateral lobectomy as a rule has been considered contraindicated in humans. For bilateral temporal lesions resistent to other therapies there is a difficult dilemma for the clinician whether to advise the patients to take the risk of operation or leave them to die of the disease.

Case report. A 43-year-old housewife was first seen in July 1980 when undifferentiated nasopharyngeal carcinoma was diagnosed.

The tumor was still confined to nasopharynx and a radical course of radiation therapy was given with 4.5 MV photons via two lateral opposed fields supplemented by one anterior field (all fields treated at each setting). Due to serious shortage of treatment machines an unconventional fractionation schedule was used; 4.2 Gy per fraction, twice weekly for 12 fractions. The biologically equivalent dose in the most infero-medial parts of both temporal lobes was equal to 1 861 in terms of Nominal Standard Dose (2) and 121 in terms of biologically effective dose assuming $\alpha/\beta = 3$ (3). She achieved complete remission and remained relapse-free.

Eight years later she began to have impaired memory and then got fever, headache, vomiting, and confusion with subacute onset. Here consciousness level slightly improved after dexamethasone but neurological examination still showed disorientation, bilateral papilledema and mild left-sided hemiparesis. Computed tomography (CT) revealed a huge roundish hypodense area in the right temporal lobe (Fig. 1). The lesion caused mass effect but showed no enhancement after contrast injection.

At right-sided craniotomy in October 1988, a cyst-like lesion containing 100 ml of yellowish-green fluid was found in the temporal lobe and anterior lobectomy was performed. The dissection extended medially to the temporal horn of the right lateral ventricle, posteriorly to 2 cm from the vein of Labbe and superiorly to 1 cm from the Sylvian veins. Histological examination confirmed the clinical diagnosis of radionecrosis and culture of the aspirated fluid did not suggest any infections. The patient regained full orientation and motor function after the operation. Steroid treatment was tailed off in December 1988 and she was able to resume her normal daily activities. In June 1989, she complained of right-sided deafness after an episode of otitis media. It was difficult to tell whether there was a neurogenic element in addition to the conductive cause. CT in May 1990 revealed an irregular hypodense area in the left temporal lobe in addition to the residual hypodensity in the right lobe (Fig. 2). There was no evidence of mass effect and the patient remained asymptomatic. In November 1991, she became very talkative and CT showed that the left-side lesion had grown into a roundish cyst with slight mass effect. No definitive treatment was offered since it was feared that surgical resection might lead to unacceptable morbidity.

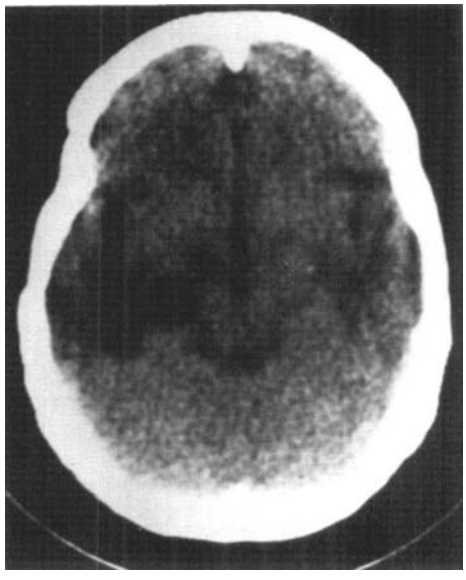

Fig. 2. CT in 1990 showing an irregular hypodense lesion in the left temporal lobe in addition to residual hypodensity in the right temporal lobe.

She was then observed until April 1992 when she became totally disorientated and CT showed further increase of the mass effect caused by the lesion in the left temporal lobe (Fig. 3). A huge cyst with yellow viscous fluid was found on exploration and left temporal lobectomy was finally performed. The dissection extended medially to the medial tip of the temporal lobe, posteriorly to the vein of Labbe and superiorly to the superior temporal gyrus. Pathological examination again revealed features consistent with radionecrosis, namely focal necrosis in cerebral cortex with replacement by fibrin and hemorrhage, marked intimal fibrinoid changes in blood vessels, gliosis and degeneration of cortical neurons in the adjacent viable brain.

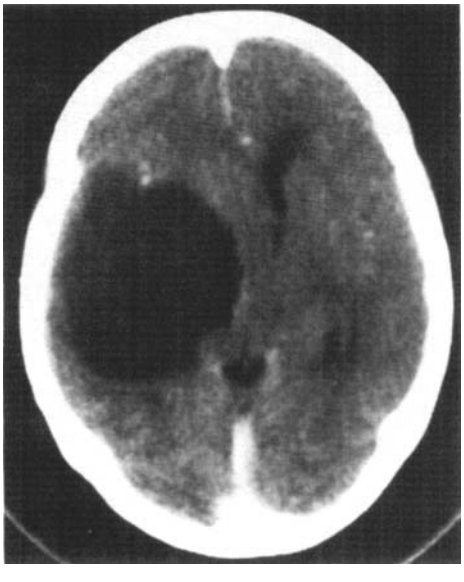

Fig. 1. CT in 1988 showing a huge roundish non-enhanced hypodense lesion in the right temporal lobe.

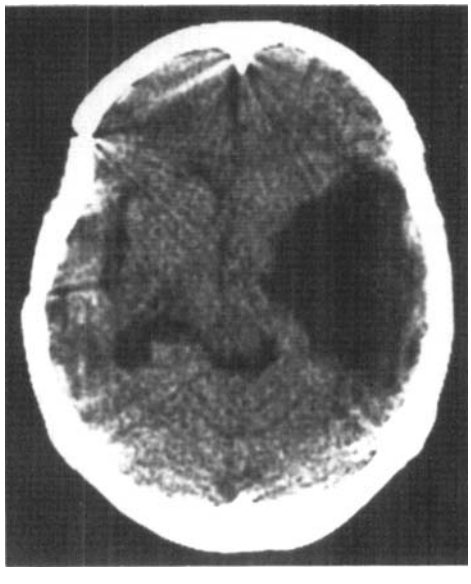

Fig. 3. CT in 1992 showing that the irregular hypodense lesion in the left temporal lobe had grown into a cyst with increasing mass effect.

During the immediate postoperative period she remained disorientated and developed left-sided deafness but to the relief and surprise of all she gradually improved and could even perform housework independently. No abnormal behavior had been observed. At the latest examination in September 1992 she was fully orientated and there were no gross neurologic deficits except for bilateral deafness. It was, however, impossible to assess her memory, intellect or olfactory functions due to communication problems.

Discussion. The classical Kluver-Bucy syndrome consists of hypersexuality, oral hyperactivity, hypermetamorphosis, placidity or aggression, memory disorder, and visual agnosia (1). To avoid this tragic outcome it is understandable that clinicians are reluctant to offer bitemporal lobectomy, even in life-saving situations with no effective alternative. The exact risk of bilateral resection in humans is poorly known as only one case has been reported in the literature (4). The incidence of Kluver-Bucy syndrome following unilaterial excision is extremely low: among the thousands of patients operated on with standard anterior temporal lobectomy for epilepsy only one case with a partial syndrome has been reported (5). Among the rare cases of this syndrome in humans the commonest etiology is bilateral temporal lobe damage due to viral encephalitis, trauma, Pick's disease, Alzheimer's disease, multiple infarction or subarachnoid cysts.

The risk of damaging the temporal lobes during radical radiation therapy for nasopharyngeal carcinoma, the peculiar clinical and CT features, and the treatment results for radionecrosis have been presented in a previous publication (6). Although the CT manifestations are often asymmetrical and non-synchronous, the basic damage is bilateral. With accumulation of long-term survivors, temporal lobe radionecrosis has been detected in 3% (n = 207) of patients with nasopharyngeal carcinoma irradiation in our institute. None has developed Kluver-Bucy syndrome. The relative scarcity of symptoms and signs in our patients is not fully understood but can possibly be attributed to the very slow rate of progression. It seems not illogical to postulate that removal of sections of the brain which have long ceased to function may not result in disastrous exacerbation of disability.

There is little doubt that surgery is the most definitive treatment for radionecrosis but the bilateral involvement poses special difficulty. Thus only ten of our patients had surgical intervention which in all cases was limited to the side with the predominant lesion. The control by unilateral surgery is, however, only temporal as relapse in the contralaterial side will inevitably occur if the patient survives long enough. Conservative treatment with corticosteroids can achieve durable objective response in about one-third of the patients detected during the initial phase of reactive edema but is ineffective once liquefactive necrosis has developed (6). Furthermore, the hazard of fatal infection as a result of severe immunodepression is alarmingly high in our crowded environment.

Although we cannot claim that bitemporal lobectomy is a safe procedure and the patient reported had not been subjected to thorough psychometric assessment, her recovery to independent normal life is gratifying. For patients severely disabled by chronic lesions not treatable by other methods the risk of surgery is well justified.

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IgD PRODUCING IMMUNOCYTOMA

A 46-year-old woman was admitted to our hospital because of fever, dyspnea, dry cough of 3-week duration and history of weight loss of 10 kg during the last year. Sixteen months before admission, she underwent a tumorectomy and axillary lymph node dissection followed by local radiation therapy for a 3 cm intraductal papillary carcinoma of the right breast. Physical exampination revealed pleural and pericardial rubs as well as massive splenomegaly. Laboratory studies revealed a hematocrit of 24%, reticulocyte count 3% and the white blood cell count was $2 \cdot 10^9$/l (56% neutrophils, 36% lymphocytes and 8% monocytes). The platelet count was $90 \cdot 10^9$/l and the erythrocyte sedimentation rate 57 mm/h (Westergren). Antinuclear, antimitochondrial and antismooth muscle antibodies were negative as well as direct and indirect coomb's tests. Serum C3 and C4 levels were normal, albumin 23 g/l, globulin 90 g/l, lactate dehydrogenase 400 IU/ml. Immunodiffusion studies of serum protein showed an IgD component at a concentration of 6 g/l and low levels of the other immunoglobulins (IgG = 2 g/l, IgA = 180 mg/l and IgM 20 mg/l); Kappa and Lambda chains were undetectable. Urine electrophoresis and immunoelectrophoresis was normal. A chest x-ray showed cardiomegaly and bilateral pleural effusions. Computed tomographic scans of the chest and abdomen showed pleuropericardial effusions and massive splenomegaly without thoracic or abdominal lymphadenopathy. Thoracentesis revealed a clear fluid with $250 \cdot 10^6$ white cells/l (91% lymphocytes, 8% neutrophils, 1% eosinophils). All cultures for bacteria, myco-bacteria, viruses and yeasts were negative as well as serological titers for mycoplasma, legionella, cytomegalovirus. A pleural biopsy showed reactive mesothelial hyperplasia with no evidence of malignancy. Biopsy of the liver was normal and bone marrow biopsy showed normal erythroid and myeloid series with 10% plasma cells. The patient underwent a laparotomy, and splenectomy was performed. The spleen weighed 1.9 kg and histological examination showed numerous non-necrotizing granulomas and diffuse infiltration by small lymphocytes and plasma cells containing 'Dutcher-bodies'. Numerous Russell bodies and rare immunoblasts were also found. The immunoperoxidase staining on paraffine-fixed tissue showed diffuse cytoplasmic positivity with anti IgD but negative with anti IgG, IgA, IgM, Kappa and Lambda chains. These findings were diagnostic of an IgD lymphoplasmacytic lymphoma (immunocytoma in Kiel classification, equivalent to the low-grade malignant lymphoma, small lymphocytic, plasmacytoid, in the International Working Formulation classification). The patient refused further investigation or therapy and was lost to follow-up.