PAPERS AND SHORT REPORTS

Treatment with gonadotrophin releasing hormone analogue in advanced prostatic cancer

J H WAXMAN, J A H WASS, W F HENDRY, H N WHITFIELD, G M BESSER, J S MALPAS, R T D OLIVER

Abstract

Repeated administration of long acting analogues of gonadotrophin releasing hormone diminishes gonadal function and in men decreases testosterone concentrations; for this reason the effect of the analogue buserelin was studied in prostatic carcinoma. Twelve consecutive patients with newly diagnosed locally advanced or metastatic carcinoma of the prostate were treated. Each patient received intranasal buserelin in divided dosages of either 600 or 1000 μg daily. Suppression of the gonadotrophins and testosterone occurred in all patients. Objective and subjective signs of regression of disease were seen in nine patients.

Buserelin offers an effective treatment of metastatic prostatic cancer without the side effects and cardiovascular risks associated with oestrogen treatment.

Introduction

It is 40 years since the original observation that orchidectomy could produce a sustained remission in prostatic cancer. Subsequently many hormone treatments have been described that induce a high incidence of initial response and symptomatic relief, but each has disadvantages and none confers a survival advantage.[1 2] As an alternative to orchidectomy administration of stilboestrol is the most commonly used, but the incidence of intolerance may reach 40% and mortality may be 20% in patients with previous myocardial ischaemia.[3] Chemotherapy has no useful role,[4 5] and only the antiandrogen progestogen cyproterone acetate appears to be as effective as stilboestrol, with fewer side effects.[6]

A radically different approach, without apparent toxicity, is the use of highly potent analogues of gonadotrophin releasing hormone. Although initially promoting increased secretion of gonadotrophin, with long term use these analogues decrease synthesis and secretion of gonadotrophin, leading to a fall in gonadal hormone concentrations.[7 8] In addition, there may be a direct inhibitory effect on the gonad.[9] Effectively, in men the pituitary-testicular axis is down regulated. Initially, workers were most interested in the contraceptive application of these compounds, and most experience in Europe has been with buserelin (D-ser[6]-ter-butyl-gonadotrophin-releasing hormone-ethylamine).[7 8] In view of the hormonal dependence of prostatic cancer the usefulness of these analogues in the management of this tumour is of interest. A preliminary clinical study of 10 patients treated with either D-ala[6]-GnRH ethylamine or buserelin was encouraging.[10] We report a detailed prospective study of 12 consecutive new patients with advanced disease treated with buserelin for up to nine months.

Patients and methods

Twelve patients gave informed consent to be treated in this study. All had histologically proved symptomatic advanced prostatic cancer for which no specific treatment had been given. Three patients had previously had myocardial infarcts. Table I gives details of the patients.

Before treatment the following were performed in each patient: full blood count; erythrocyte sedimentation rate; liver function tests; measurement of calcium, phosphate, urea, creatinine, and electrolyte concentrations; *x* ray films of the chest and pelvis; computed tomography of the pelvis; and a radioisotope bone scan. Patients were staged according to the 1978 TNM classification of the International Union Against Cancer.[11] After basal blood samples had been taken for measurement of concentrations of prolactin (mean of three readings), sex hormone binding globulin, testosterone, 17-β-oestradiol,

St Bartholomew's Hospital, London EC1

J H WAXMAN, BSC, MRCP, Imperial Cancer Research Fund research fellow, department of medical oncology
J A H WASS, MD, MRCP, senior lecturer, department of endocrinology
W F HENDRY, CHM, FRCS, consultant urologist
H N WHITFIELD, MCHIR, FRCS, consultant urologist
G M BESSER, DSC, FRCP, professor of endocrinology
J S MALPAS, DPHIL, FRCP, professor of medical oncology
R T D OLIVER, MD, MRCP, senior lecturer, Medical College (and at Institute of Urology)

Correspondence to: Dr J H Waxman.

TABLE I—*Details of patients*

Case No	Age (years)	Disease staging[11]	Tumour differentiation
1	74	$T_2N_0M_0$	Well differentiated
2	69	$T_2N_1M_1$	Well differentiated
3	65	$T_3N_0M_1$	Moderately differentiated
4	59	$T_2N_XM_1$	Poorly differentiated
5	77	$T_2N_1M_1$	Well differentiated
6	68	$T_3N_0M_1$	Well differentiated
7	62	$T_2N_2M_1$	Well differentiated
8	72	$T_4N_1M_1$	Moderately differentiated
9	76	$T_2N_XM_0$	Well differentiated
10	57	$T_4N_0M_1$	Moderately differentiated
11	61	$T_3N_0M_0$	Moderately differentiated
12	50	$T_4N_2M_1$	Poorly differentiated

TABLE II—*Response to treatment*

Case No	Regimen (μg/day) (treatment duration)	Symptoms		Interval to response
		At presentation	With treatment	
1	600 μg (1 month)	Urinary frequency (nocturia × 6)	No response	
2	600 μg (9 months)	Urinary frequency (nocturia × 6)	Nocturia × 3	3 weeks
		Bone pain	Resolved	3 weeks
		Oedema	Resolved	3 weeks
3	600 μg (9 months)	Urinary frequency (daytime, every 30 min)	Resolved (daytime, every 4 h)	2 weeks
4	600 then 1000 μg (3 then 2 weeks)	Urinary frequency (nocturia × 4)	No response	
5	600 then 1000 μg (5 then 3 weeks)	Urinary frequency (nocturia × 4)	No response	
		Bone pain		
6	1000 μg (6 months)	Bone pain	Resolved	3 days
		Paraplegia (treatment with dexamethasone and laminectomy failed)	Walking	12 days
		Urinary retention	Resolved	3 days
7	1000 μg (5 months)	Nodal secondaries	Impalpable	3 weeks
		Urinary frequency (nocturia × 4)	Nocturia × 1	
8	1000 μg (4 months)	Urinary retention	Resolved	1 week
9	1000 μg (6 months)	Urinary frequency (nocturia × 3)	Nocturia × 1	2 weeks
10	1000 μg (6 months)	Urinary frequency (daytime, hourly)	Daytime × 4	2 weeks
		Weight loss	Regained	1 month
		Malaise	Resolved	2 weeks
11	1000 μg (7 months)	Urinary retention	Resolved	2 weeks
		Weight loss	Regained	8 weeks
12	1000 μg (4 months)	Leucoerythroblastic anaemia	Resolved	4 weeks
		Urinary frequency (nocturia × 5)	Nocturia × 2	1 week
		Weight loss	Regained	6 weeks

progesterone, and growth hormone a standard gonadotrophin releasing hormone test (100 μg) was performed. Concentrations of luteinising hormone, follicle stimulating hormone, growth hormone, and prolactin were measured by specific double antibody radioimmunoassays using Medical Research Council standards 68/40, 78/549, 66/217, and 75/504 respectively. After ether extraction concentrations of testosterone and 17-β-oestradiol were measured by tritiated radioimmunoassays. Progesterone concentration was measured by tritiated radioimmunoassay after hexane extraction. Sex hormone binding globulin concentration was measured by saturation radioimmunoassay.[12] In four patients concentrations of testosterone, luteinising hormone, and follicle stimulating hormone were measured daily for one week and weekly for the first month of treatment. In the remaining eight patients these concentrations were measured weekly.

All the investigations were repeated after one month's treatment and the patients' responses assessed. All abnormal findings were reassessed at monthly intervals together with concentrations of circulating testosterone, luteinising hormone, and follicle stimulating hormone. In patients in whom bone scans showed evidence of metastases the scans were repeated at monthly intervals.

After preliminary assessment treatment was started with buserelin. The first five patients received 200 μg buserelin intranasally every eight hours. In three patients (cases 1, 4, and 5), however, suppression of testosterone and relief of symptoms was not complete, and so in two of these (cases 4 and 5) the dosage was increased to 200 μg five times daily; the testosterone concentration fell into the range seen in patients who have been castrated. The two patients who had responded to the lower dose were maintained on it. All the patients subsequently entering the study received 200 μg five times daily. Treatment was given for between one and nine months.

Results

Nine of the 12 patients achieved objective and subjective signs of regression of disease (table II). Two of the five patients (cases 2 and 3) initially treated with 600 μg buserelin daily responded to treatment. Two patients (cases 4 and 5) with partial initial suppression of serum testosterone concentrations showed a reduction in concentration into the range in men who have been castrated at a dose of 1000 μg daily without relief of their symptoms. All seven patients initially treated with 1000 μg daily responded to treatment.

Computed tomography—Treatment resulted in objective improvement in six patients (cases 3, 6, 8, 10, 11, and 12), including a decrease in prostatic size, a diminution in lymphadenopathy (fig 1), a resolution of sclerotic and lytic deposits, and improved separation of the seminal vesicles. In three patients (cases 1, 2, and 5) no changes occurred in the scans with treatment.

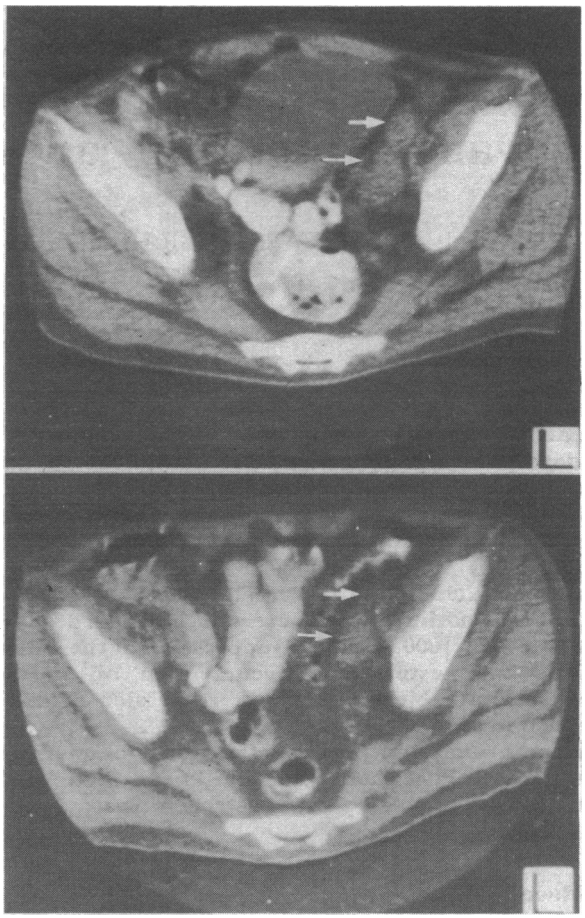

FIG 1—Computed tomograms showing diminution in lymphadenopathy that occurred with treatment.

Isotope bone scanning—Eight patients had evidence of bone metastases. Four (cases 2, 6, 7, and 10) showed improvement with treatment, but none achieved a normal scan.

Acid phosphatase activity was initially raised in six patients (cases 2, 4, 5, 7, 10, and 12) and became normal in five (cases 2, 5, 7, 10, and 12) within one to three months (mean 1·4 months). One patient (case 4), who had an undifferentiated tumour, had a persistently raised acid phosphatase activity, which did not improve. In case 5 the symptoms failed to respond to treatment but normal acid phosphatase activity was achieved.

HORMONAL CHANGES

Serum testosterone—The two treatment regimens produced appreciably different testosterone suppression (fig 2). After one month's treatment mean serum testosterone concentration had decreased by 59% from 12·1 nmol/l (3·5 ng/ml) (range 10·0-14·0 nmol/l (2·9-

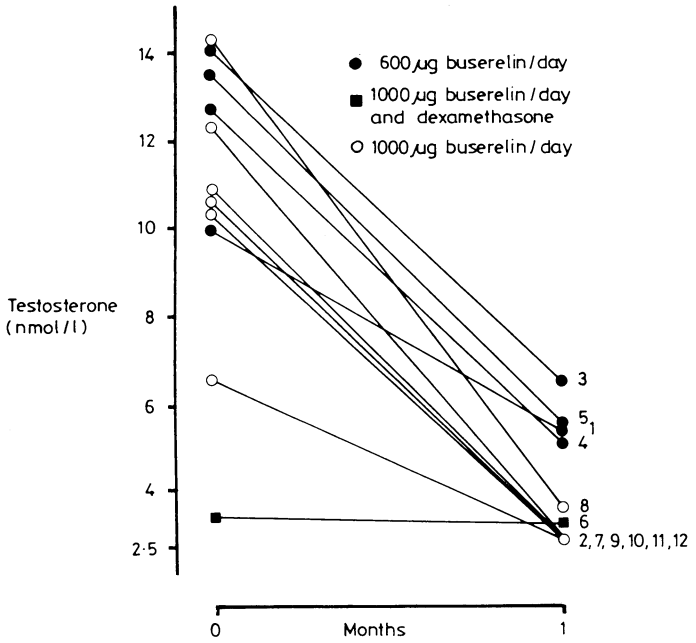

FIG 2—Testosterone concentrations before and after one month of treatment (normal range 10-38 nmol/l (2·9-11·0 ng/ml)).

Conversion: SI to traditional units—Testosterone: 1 nmol/l ≈ 0·28 ng/ml.

4·0 ng/ml)) to 5·0 nmol/l (1·4 ng/ml) (range 3·6-6·4 nmol/l (1·0-1·8 ng/ml)) with the 600 µg regimen and by 73% from 9·9 nmol/l (2·9 ng/ml) (range 3·1-12·5 nmol/l (0·9-3·6 ng/ml)) to 2·7 nmol/l (0·8 ng/ml) (range <2·5-3·9 nmol/l (<0·7-1·1 ng/ml)) with the 1000 µg regimen (Wilcoxon's rank sum test on unpaired samples $p < 0.05$). With the 1000 µg regimen concentrations seen in castrated patients were reached by the fourth treatment week.

Luteinising hormone—After one month's treatment the mean luteinising hormone concentration had decreased by 59% from 8·8 U/l (range 1·8-23·5 U/l) to 3·6 U/l (range 2·2-6·0 U/l) ($p < 0.01$). There was no difference in concentration between patients who did and did not respond or between the 600 µg and 1000 µg regimens.

Follicle stimulating hormone—After one month's treatment the median concentration of follicle stimulating hormone had decreased by 42% from 5·7 U/l to 3·3 U/l (not significant). There was no difference in concentrations between patients who did and did not respond or between the 600 µg and 1000 µg regimens.

17-β-Oestradiol—After one month's treatment the mean 17-β-oestradiol concentration had decreased by 25% from 137 pmol/l to 103 pmol/l ($p < 0.05$). A significant difference ($p < 0.05$) was found when the changes in concentrations produced by the two treatment regimens were compared: the mean 17-β-oestradiol concentration decreased by 10% from 132 pmol/l to 119 pmol/l with the 600 µg regimen and by 49% from 164 pmol/l to 83 pmol/l with the 1000 µg regimen. Oestrogen concentrations were not different between patients who did and did not respond.

Prolactin—After one month's treatment the mean prolactin concentration had decreased by 56% from 292 mU/l to 129 mU/l ($p < 0.05$). No significant difference was found between patients who did and did not respond or between the 600 µg and 1000 µg regimens.

Progesterone, growth hormone, and sex hormone binding globulin concentrations did not change significantly with treatment.

SIDE EFFECTS OF TREATMENT

All of the patients complained of inability to attain erections. They also noted that facial flushing occurred from one to six times daily; this was mild and lessened in intensity and frequency as the duration of treatment increased.

Discussion

This study has shown that buserelin, the long acting analogue of gonadotrophin releasing hormone, suppressed secretion of testosterone and gonadotrophin in advanced prostatic cancer, improving several of the symptoms and signs—namely, bone pain, urinary frequency, lymphatic obstruction, nodal deposits, leucoerythroblastic anaemia, and cord compression—often to the point of complete resolution.

A hypothalamic factor, a decapeptide originally described in 1969, releases both luteinising hormone and follicle stimulating hormone.[13] Its release from the hypothalamus is pulsatile, and this pulsatility is important for both the synthesis and secretion of the gonadotrophins by the pituitary.[14] Subsequently, substituted analogues of gonadotrophin releasing hormone were described that seemed to possess greatly enhanced potency.[15] It was initially thought that these analogues would be of clinical use in syndromes of gonadotrophin deficiency,[16] but this was not so because the mechanism of action of long acting analogues of gonadotrophin releasing hormone is paradoxical. After initial stimulation down regulation of the pituitary and finally also the gonad occurs, resulting from the prolonged binding of the analogues to pituitary receptors.[17] Thus the gonadotrophin analogues have a clinical role in suppressing gonadal activity, and they have been used as contraceptives[18] and in endometriosis,[19] in precocious puberty,[20] and breast cancer.[21]

In a previous series of patients the clinical effect of superactive gonadotrophin analogues in prostatic cancer was assessed. In six patients with locally advanced disease and four with metastatic prostatic cancer were given D-Trp^6-substituted analogues subcutaneously and D-ser^6-substituted analogues subcutaneously or intranasally. Evidence of response was observed in nine patients.[10]

It is not obvious which effect of treatment is important in mediating response. In our patients response did not relate to concentrations of circulating gonadotrophins, testosterone, or oestradiol, and this is true also for treatment with oestrogens or castration.

This study clearly established that buserelin is as effective, at least in the short term, as stilboestrol or orchidectomy. Its advantages over other medical treatment are that it is specific in terms of suppression of gonadotrophin and gonadal steroids, obviates the need for surgery, and is without major side effects. Its long term efficacy requires evaluation and comparison with that of stilboestrol.

We thank Miss Lisa White and Mrs Jo Barton for editorial help; Mr Walter Gregory, who provided statistical guidance; Mr P Barry and Drs G Jagger, P Reeve, and J Walker, who helped with the organisation of the patients; Profosser L Rees and Mr L Perry for the hormone assays; Dr F E White, who reviewed the computed tomograms; the staff of Rees Mogg and the day wards; and the patients who took part in the study. Drs T A Lister and P F M Wrigley kindly commented on the manuscript.

References

1 Blackard CE, Byar DP, Jordan WP, and the VACURG. Orchiectomy for advanced prostatic carcinoma: a reevaluation. *Urology* 1973;**1**:553-60.
2 Lepor A, Ross A, Walsh PC. The influence of hormonal therapy on survival of men with advanced prostatic cancer. *J Urol* 1982;**128**:335-40.
3 The Coronary Drug Project Research Group. The coronary drug project. Initial findings leading to a modification of its research protocol. *JAMA* 1970;**214**:1303-13.
4 Citrin DL, Hogan TF. A phase II evaluation of adriamycin and cis-platinum in hormone resistant prostate cancer. *Cancer* 1982;**50**:201-6.
5 Schmidt JD, Scott WF, Gibbons R, *et al.* Chemotherapy programs of the national prostatic cancer project. *Cancer* 1980;**45**:1937-46.
6 Peeling B. Castration for prostatic carcinoma. Still an alternative form of treatment. In: Schroeder F, ed. *Proceedings of an international symposium of androgens and anti-androgens.* Netherlands: Schering, 1983.
7 Bergquist C, Nillius SJ, Bergh T, Skarin G, Wide L. Inhibitory effects on gonadotrophin secretion and gonadal function in men during chronic treatment with a potent stimulatory luteinising hormone-releasing hormone analogue. *Acta Endocrinol* 1979;**91**:601-8.
8 Bergquist C, Nillius SJ, Wide L. Inhibition of ovulation in women by intranasal treatment with a luteinising hormone-releasing hormone agonist. *Contraception* 1979;**19**:497-504.
9 Labrie F, Auclair C, Cusan L, Kelly PA, Pelletier G, Ferland L. Inhibitory effect of LHRH and its agonists on testicular gonadotrophin receptors and spermatogenesis in the rat. *Int J Androl* 1978;**2**:303-18.

[10] Tolis G, Ackman D, Apostolos S, *et al.* Tumour growth inhibition in patients with prostatic carcinoma treated with luteinizing hormone releasing hormone agonists. *Proc Natl Acad Sci USA* 1982;**79**:1658-62.
[11] Wallace DM, Chisholm GD, Hendry WF. TNM classification for urological tumours (UICC). *Br J Urol* 1979;**47**:1-12.
[12] Fattah DI, Chard T. Method for measuring sex hormone binding globulin. *Clin Chem* 1981;**27**:1277-9.
[13] Kastin AJ, Schally AV, Gual C, Midgley AR, Bowers CY, Diaz-Infante A. Stimulation of LH release in men and women by LH-releasing hormone purified from porcine hypothalami. *J Clin Endocrinol Metab* 1969;**29**: 1046-50.
[14] Belchetz PE, Plant TM, Nakai Y, Keogh EJ, Knobil E. Hypophysial response to continuous and intermittent delivery of hypothalamic gonadotrophin releasing hormone. *Science* 1978;**202**:631-3.
[15] Coy DH, Schally AV. Gonadotrophin releasing hormone analogues. *Ann Clin Res* 1978;**10**:139-44.
[16] Tharandt L, Schulte H, Benker G, Hackenberg K, Reinwein D. Treatment of isolated gonadotrophin deficiency in men with synthetic LH-RH and a more potent analogue of LH-RH. *Neuroendocrinology* 1977;**24**:195-207.
[17] Swift AD, Crighton DB. Release activity plasma elimination and pituitary degradation of synthetic luteinizing hormonal releasing hormone and its analogues. *J Endocrinol* 1978;**77**:35P.
[18] Linde R, Doelle GC, Alexander N, *et al.* Reversible inhibition of testicular steroidogenesis and spermatogenesis by a potent gonadotrophin-releasing hormone agonist in normal men. *N Engl J Med* 1981;**305**: 663-7.
[19] Meldrum DR, Chang RJ, Lu J, Vale W, Rivier J, Judd HL. "Medical oophorectomy" using a long acting GnRH agonist—a possible new approach to the treatment of endometriosis. *J Clin Endocrinol Metab* 1982;**54**:1081-3.
[20] Laron Z, Kauli R, ben Zeer Z, Comara-Schally AM, Schally AV. D-Trp6 analogue of luteinising hormone releasing hormone in combination with cyproterone actetate to treat precocious puberty. *Lancet* 1981;ii: 955-6.
[21] Klijn JGM, de Jong FH. Treatment with a luteinizing hormone releasing-hormone analogue (buserelin) in premenopausal patients with metastatic breast cancer. *Lancet* 1982;i:1213-6.

(*Accepted 22 February 1983*)

Traumatic neuropathy of second cervical spinal nerves

SIMON BEHRMAN

Abstract

The second cervical spinal nerves are unduly vulnerable to forcible approximation of the arches of the atlas and axis and to excessive rotation of the atlas on the axis. Sequelae of such injury include sensory aberrations ranging from loss of feeling to severe neuralgia and disorders of balance.

Diagnosis of second cervical neuropathy may be difficult when there are multiple injuries to the cervical spine, but most cases clear up spontaneously within one to three years.

Introduction

Occipital neuralgia was recognised in the nineteenth century and descriptions of the condition may be found in contemporary textbooks. It was attributed to an "affection" of the great occipital nerve until Charles Toogood Downing observed that "the Earl of . . ., a nobleman of strong constitution, was not relieved of cervico-occipital neuralgia when the sub-occipital nerve was divided by Mr Syme." This led Downing to suggest that occipital neuralgia was due to damage to the second cervical nerve.[1] A century later Hunter and Mayfield provided the anatomical explanation why the second cervical nerves are particularly susceptible to trauma.[2] Unlike the other spinal nerves, they are not protected by bony pedicles and facets. Their ganglia lie on the vertebral arch of the axis and the nerves pass between the arches of the atlas and the axis to the soft tissues in the neck. Hence they are clearly vulnerable and may be crushed when the two bony surfaces are approximated by forced hyperextension of the head. They may also be injured when excessive rotation occurs in one direction and the arches of the atlas and axis exert a scissor like action on the ipsilateral nerve. Thus both hyperextension and excessive rotation may result in injury to one or both of the second cervical nerves. Wrenching movements of the head are particularly dangerous since they combine both movements.

London

SIMON BEHRMAN, FRCP, consultant emeritus in neurology, Guy's Hospital

Correspondence to: 33 Harley Street, London W1N 1DA.

Case report

A young waitress was a front seat passenger when her car was hit at high speed by another car coming from the opposite direction. She was not wearing a seat belt and was thrown forward and upward and then violently backwards. She was taken to hospital complaining of severe headache and dizziness and her neck was immobilised in a collar. She returned to work three months later. She was still having symptoms, however, which were in the form of sharp, intermittent headaches originating in the nape of the neck and radiating to the right temple and dizzy spells associated with nausea and loss of balance. (On one occasion when she was spooning cream on to a customer's pudding she suddenly lurched to one side and spilt cream all over his tie.) Examination showed diminished sensation to pin prick in the territory of the right second cervical spinal nerve and tenderness over the right great occipital nerve.

Review of 17 cases of post-traumatic neuropathy of the second cervical spinal nerve disclosed 12 that were caused by similar such acceleration-deceleration road traffic accidents. In the remainder the initiating trauma was less severe, and in two patients the injury occurred when the head was violently turned to one side to avoid a threat to the eyes.

Comment

Injury to the second cervical spinal nerve is associated with sensory aberrations usually associated with disturbances of equilibrium. The sensory aberrations range from loss of sensation to severe neuralgia, and the pain is often burning or stabbing. It tends to be intermittent, and associated with superficial tenderness of the scalp, which may be noticed on brushing the hair. The sensory changes may be hemicranial or localised to fixed areas within the distribution of the second cervical nerve —for example, periorbital, temporal, suboccipital, or, in rare cases, around the ear or at the angle of the jaw. Tenderness on palpation of the greater occipital nerve is common. The condition is usually unilateral, and in the rare cases of bilateral nerve damage the sensory abnormalities are usually asymmetrical.