

INHERITED CANCER SYNDROMES SHOULD BE CONSIDERED IN YOUNG PATIENTS WITH NEWLY DIAGNOSED HEAD AND NECK CANCER

I read with interest the article ‘Head and neck cancer’ (Casasola RJ. *J R Coll Physicians Edinb* 2010; 40:343–5) and would like to give some comments.

First, while this may have been beyond the scope of the article, the author did not mention inherited cancer syndromes such as Fanconi anaemia (FA), Li Fraumeni syndrome, Bloom syndrome, ataxia telangiectasia, dyskeratosis congenita and xeroderma pigmentosa as aetiological factors for head and neck cancers.^{1,2} The recognition of those inherited cancer syndromes, especially of FA, is important for the following reasons.

Typically, patients with inherited cancer syndromes present with head and neck cancers at a young age. The median age of classical FA diagnosis is seven years and usually FA diagnosis precedes cancer diagnosis by several years (median age for leukaemia is 16 years, whereas that for solid tumors including head and neck cancers is 26 years). Occasionally, they do not have characteristic features and FA diagnosis is delayed for several years. Cancer diagnosis often precedes the diagnosis of FA by a few years. One study shows that in 25% of patients with FA with cancers, cancer diagnosis precedes FA diagnosis.

Head and neck cancer may be the initial presentation of FA.³ Management of head and neck cancer in this patient population is different as FA patients are extremely sensitive to both chemotherapy and radiotherapy, which can lead to severe myelosuppression and mucositis. It is therefore very important to establish a diagnosis of FA before initiating cancer treatment. Management by surgical resection with clear margins is preferred. If surgery is contraindicated, dose-adjusted radiotherapy may be employed.⁴ Attempts to use standard multimodality treatment, including chemotherapy and radiotherapy, would probably have been very toxic and perhaps lethal to those patients.³

Secondly, those patients with inherited cancer syndromes are also at very high risk for second neoplasms. For example, FA patients are also at risk of myelodysplastic syndromes, acute leukaemia, other aerodigestive tract cancers, gynaecological, skin and bone cancers.⁵ It is also important to watch out for the development of new second primary cancers in those patients.

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Author's reply

I am grateful to Dr Oo for his comments and am in complete agreement with his thoughts. The inherited cancer syndromes as aetiological factors in head and neck cancer should perhaps have been included for completeness. The main thrust of this article, however, was to highlight the role of human papillomavirus and the changing aetiology in head and neck cancer to our non-head and neck specialist colleagues, and hopefully this has been achieved.

Dr RJ Casasola

ANTIPHOSPHOLIPID SYNDROME AS CAUSE OF COGNITIVE DECLINE OR DEMENTIA IN THE ELDERLY

The symposium review by Professor Black on vascular cognitive impairment was very informative (Black SE. *J R Coll Physicians Edinb* 2011; 41:49–56), but I would like to point out that antiphospholipid antibody syndrome (APS) in the elderly is yet another (perhaps modifiable) vascular risk factor for stroke. While it is estimated that about 50% of strokes below 50 years of age are caused by APS, data from the Euro-Phospholipid Project Group documented 2.5% prevalence for multi-infarct dementia in APS.¹ Micro-infarcts in APS do seem to occur in the strategic areas that would lead to cognitive decline or dementia and modern imaging techniques also show metabolic impairments that correlate to progressive dementia with the presence of antiphospholipid antibodies.²

Antiphospholipid antibody syndrome is an autoimmune prothrombotic condition and requires one major clinical criterion (recurrent venous/arterial thromboses, or multiple pregnancy morbidity) and one laboratory criterion (presence of antiphospholipid antibodies, i.e., anticardiolipin or lupus anticoagulant present on at least two occasions >12 weeks apart) for diagnosis. Primary APS denotes no underlying disease but has the potential to evolve; secondary APS is usually related to systemic lupus erythematosus (SLE). Microangiopathic APS can present with retinal vascular thrombosis, skin lesions, nailfold splinter haemorrhages, bowel ischaemia, hearing loss or osteonecrosis. A wide spectrum of neurological features has been described in APS, which includes transient ischaemic attacks and strokes, epilepsy, chorea, psychiatric features, multiple sclerosis-like lesions on imaging, dementia and overlap with ischaemic stroke in Sneddon's syndrome with severe dementia.^{3,4}

Few studies have systematically analysed the onset of dementia in APS patients, but cognitive deficits that lead to cognitive decline seem to be already present in some patients at first diagnosis of APS. Forty-two percent of patients in the study by Tektonidou and colleagues had cognitive deficits in the form of complex attention deficits or verbal fluency, but none were diagnosed with dementia.⁴ A significant association between cognitive deficits and the presence of livedo reticularis and white matter lesions on magnetic resonance imaging in the same study supported the hypothesis that cerebral microvasculopathy may be the underlying mechanism for cognitive dysfunction.

Gómez-Puerta and colleagues reviewed the literature from 1983 to 2003 and found 30 patients with dementia and APS (including five of their own) and concluded that dementia was an unusual finding but a disability that had significant impact on the patient's activities of daily living.³ The mean age of the patients was 49±15 years (range 16–79 years) and a third of patients had SLE, 63% had cortical infarcts, 30% basal ganglia infarcts and 37% had signs of cerebral atrophy on imaging studies.

The concept of 'triple positivity' has been proposed, i.e., the co-existence of lupus anticoagulant, high titre anticardiolipin antibodies and anti-β2 GPI antibodies that pose a higher risk for thrombotic events than single or double positivity; an odds ratio (OR) of 33.3 in triple-positive patients compared with 2.2 in double positives with the absence of lupus anticoagulant.⁵ Pathological values for antinuclear antibodies and increased levels of antiphospholipid antibodies significantly correlated with the presence of cerebral lesions in another study.⁶

Animal models support the theory that presence of antiphospholipid antibodies lead to cognitive decline, with another recent study showing a significant interaction between APP genotype (for Alzheimer's dementia) and the induction of APS on a female background.^{7,8} Screening for all elderly patients who present with strokes for APS would not be worthwhile, particularly as a recent study showed the limited pick-up rate, only two of 78 patients (2.5%) were found to have APS on routine screening for inherited thrombophilias.⁹

Although there is no evidence that aspirin alone is effective in treating dementia, anticoagulation with warfarin may not be a choice for everyone, particularly if there are significant co-morbidities and the risk of bleeds has to be balanced with the risk of further cognitive decline. However, the impact of dementia on daily life and prognostic consequences of untreated APS are significant, and would be significantly more when they co-exist.

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Author's reply

Dr Khan nicely outlines how antiphospholipid syndrome (APS) can cause vascular cognitive impairment (VCI) not only in younger individuals but also in the elderly. In a large European Study, APS was associated with dementia in 2.5% of cases, and while the mechanism is thought to be occlusive arterial or venous disease, direct neuronal antibodies may also play a role.¹ Given that 87% of cases were under the age of 50 in this survey, APS is an important cause of young-onset vascular dementia, a devastating disability that greatly alters the life quality and prospects in affected individuals at any age.

The low prevalence means that screening older patients for APS may not be cost-effective, but uncommon causes of VCI in the elderly must be borne in mind, especially if there are other signs suggesting collagen vascular disease. There are numerous different inflammatory and non-inflammatory vascular processes that can cause multifocal or strategic cerebrovascular brain injury leading to cognitive decline. The clinician must be vigilant about these rare aetiologies, which may require different management strategies such as the use of anticoagulants or immunosuppressants.

In noting the aetiological heterogeneity of VCI, my review also pointed out that the majority of patients with VCI have not had overt stroke, but rather covert small vessel

vasculopathy, implicating both arteriolar and venular occlusive pathologies, which can also exacerbate and reflect Alzheimer pathology or other neuro-degenerations, and accelerate clinical expression of dementia. With population ageing, not only will we increasingly see the effects of ageing, vascular risk factors and sedentary lifestyle played out in both arterioles and venules, but the rare vasculopathies will continue to take their toll. Still, vascular disease remains the most preventable cause of dementia, if only we can implement the best practices already known, and continue to search vigorously for even better ways to prevent and ameliorate the debilitating cognitive deficits resulting from vascular brain damage.

Professor Sandra E Black

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LORD MORAN AS A BIOGRAPHER OF CHURCHILL

AW Beasley's article on Lord Moran as a biographer of Winston Churchill (Churchill Moran and the struggle for survival. *J R Coll Physicians Edinb* 2010; 40:362–7) struck a chord with me.

As a student of political biography it has always seemed to me that there were discrepancies between Moran's account of Churchill's health and behaviour and other sources. By Moran, Churchill was represented as becoming senile and difficult to handle even from the middle of the Second World War. In contrast, a study of Churchill, unusually concentrating on domestic politics, states that 'from 1949 to 1953 he led the Conservative party with great skill and flair into the middle ground of politics'¹ – hardly suggestive of senility.

By chance it is possible to compare Moran's account of Churchill in a particular illness with that of another distinguished physician, Guy Scadding, later professor of medicine at the Brompton Hospital.² Scadding was a medical officer in North Africa in 1943 when he was summoned to Carthage to give a further opinion on Churchill's pneumonia, which was in fact responding well to sulphonamides. Moran's account of what happened afterwards was that 'Churchill became very difficult, savaging Bedford and Scadding who were only trying to do their job'. Scadding commented: 'I did not keep a diary, but I am sure I should not have forgotten the experience of being savaged by Churchill. A conversation did take place but without the emotional overtones, and Moran was unfair to Churchill representing him as being discourteously overbearing.'

In addition to the defects listed by Beasley, Moran seems prone to over-dramatisation and exaggeration of his

subject's difficulties. Regrettably I think non-medical historians have often regarded Moran's accounts as reliable because of his profession.

Dr GC Ferguson

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Author's reply

I am grateful to Dr Ferguson for his support of my views on Churchill and Lord Moran, and in particular for having drawn to my attention the account by Professor Scadding of his involvement in the management of Churchill's pneumonia at Carthage in 1943. This information is now enshrined in the manuscript of my medical history of Churchill, which is approaching the publication stage.

I share Dr Ferguson's views about Lord Moran's tendency to exaggeration; in part at least this is due, I believe, to the fact that he was writing to the private agenda of documenting his role, as the skilled and loyal physician, in keeping a derelict prime minister alive during the war.

The challenge for a writer on the subject of Churchill's health is to be resolute in exposing exaggeration and patient in debunking myth, without falling into the trap of developing the same meanness of spirit that Moran himself seems to have displayed on occasions. I have tried to avoid this trap in the forthcoming book – but Churchill myths, many traceable to Lord Moran, are prevalent and deeply entrenched.

I should also take this opportunity to express my thanks to a number of readers who have written directly to me, expressing their approval of my account of 'the struggle for survival'.

AW Beasley

CIRCADIAN RHYTHM SLEEP DISORDERS – A HISTORICAL PERSPECTIVE

Recent correspondence (*J R Coll Physicians Edinb* 41: 94) has raised questions concerning the investigation of sleep disorders that may be due to a disturbance of the circadian system. Your readers may be interested in the details of what was almost certainly the first case to be reported in literature. In 1929, Fulton and Bailey, working in the surgical clinic of Harvey Cushing, observed that the rhythm of sleep and wakefulness was disturbed in a young woman with a tumour just above the pituitary.¹ Minnie had experienced transient attacks of drowsiness for several years. She was even unable to stay awake to have her photograph taken and she would often drop off

to sleep in the company of friends, even when the conversation was said to be animated. The attacks of drowsiness became progressively more severe and more prolonged, and somnolence became almost continuous. She died at the age of 24 years.

This paper contained almost a prophesy: 'It was, perhaps, erroneous to speak of a sleep centre in the brain, but tumors above the pituitary gland may disturb the rhythm of sleep and wakefulness.' This appears to be the first suggestion in the clinical literature that the alternating pattern of sleep and wakefulness was somehow related to a specific part of the brain and, in turn, that whatever may be involved in the control of sleep and wakefulness there was a rhythmic input. Perhaps magnetic resonance imaging would have been useful in the diagnostic process.

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SALIVARY CORTISOL IN THE EVALUATION OF INCIDENTALOMAS

Although it was through the evaluation of serum cortisol that Drs Ghosh, Jones and Swaminathan were able to validate the diagnosis of cortisol secreting incidentalomas in their patients with clinically overt Cushing's syndrome (Adrenal incidentalomas: a simple guide to a disease of modern technology. *J R Coll Physicians Edinb* 2010; 40:314–6), the use of salivary cortisol might be a useful alternative strategy. It can be used not only in instances where cortisol-secreting adenomas (CSA) (which might include incidentalomas) give rise to clinically overt Cushing's syndrome,¹ but also in patients in whom Cushing's syndrome remains subclinical despite cortisol secretion by the incidentaloma.²

Where CSAs are associated with clinically overt Cushing's syndrome, sampling at 23.00 for salivary cortisol vs serum cortisol yields comparable sensitivity (97% vs 97%) and specificity (69% vs 63%).¹ Furthermore, at 23.00, highly significant differences are found between CSA subjects with clinically overt Cushing's syndrome and healthy controls ($p < 0.001$ for salivary cortisol, and $p < 0.01$ for serum cortisol),¹ perhaps giving salivary cortisol a slight 'edge'.

The picture is more complex where Cushing's syndrome remains subclinical despite the presence of a cortisol-secreting incidentaloma. In this context, both late-night

salivary cortisol and midnight serum cortisol fail to distinguish between cortisol-secreting incidentalomas and non-secreting adenomas ($p > 0.05$ for each of those tests),² despite a validation of autonomous cortisol secretion by documenting subnormal adrenocorticotropin hormone levels (ACTH) at 08.00 ($p < 0.0002$), incomplete suppression of serum cortisol after low-dose dexamethasone ($p < 0.0001$) and suboptimal cortisol circadian rhythmicity ($p < 0.006$).

Thus, given the comparable diagnostic utility of 23.00 salivary and serum cortisol in incidentaloma patients with clinically overt Cushing's syndrome¹ and equally the comparable lack of diagnostic utility of either test in incidentaloma patients with subclinical Cushing's syndrome,³ salivary cortisol sampled at 23.00 might be more advantageous as a screening test because it can be performed on an outpatient basis³ and its interpretation is not confounded by venepuncture-related stress.³ An additional refinement would be the performance of the low-dose dexamethasone test, using either serum cortisol² or salivary cortisol,⁴ and sampling of basal morning ACTH² in cases of diagnostic uncertainty.

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Authors' reply

We thank Dr Jolobe for his thoughts on the utility of salivary cortisol in the evaluation of Cushing's syndrome. We agree that measuring salivary cortisol is a simple and reliable test to evaluate the hypothalamic pituitary adrenal (HPA) axis, especially with developments in liquid chromatography mass spectrometry methods. We hope that this test will be widely available in the UK and used routinely for evaluation of the HPA axis.

Dr Krishnan Swaminathan

Please note that opinions expressed in Letters to the Editor should not be taken as those of the Editorial team or the Royal College of Physicians of Edinburgh.

Answers to the MCQ questions on page 139: 1. B 2. B 3. E 4. B