Optic neuropathy and chronic cyanide intoxication: a review

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Tobacco amblyopia

Tobacco amblyopia was first described by Beer[1] in 1817 and since then there has been much discussion and controversy concerning the precise nature of the condition. By definition, tobacco is a necessary factor, but when in 1958 we presented our clinical and pathological findings in patients seen at the Bristol Eye Hospital with classical tobacco-amblyopia visual fields, we considered that no satisfactory explanation had previously been given to certain fundamental questions we set out to answer[2]. Firstly, why do so few smokers develop this condition? Secondly, why is it that the average patient with tobacco amblyopia smokes very little more than his healthy counterpart[3,4]? Thirdly, why is it that whereas one person may be a heavy pipe-smoker for 50 years or so and yet suffer from no visual deterioration, another may develop pronounced visual failure after smoking in moderation for only a year or two?

Tobacco amblyopia is commonest in middle-aged and elderly men[3]. In 1525 cases, only 7 were women. Although cigars and cigarettes are seldom solely responsible, an opinion expressed that tobacco amblyopia does not occur in cigarette smokers is inaccurate[5]. Schepens[6] reported that during the 1939-45 War, undernourished Belgian civilians quite commonly developed tobacco amblyopia even if they smoked less than 25 cigarettes a day. This led Schepens to postulate that tobacco amblyopia was a deficiency disease, and it is certainly known that malnutrition and excessive alcohol consumption tend to increase the incidence and severity of this condition[2].

The patient with tobacco amblyopia suffers from progressive deterioration of vision in both eyes and has characteristic visual field changes. Only when visual acuity is considerably reduced is there pallor of the optic disc and an afferent pupillary defect.

The first symptom is an inability to distinguish between the colours red and green before the vision for white is materially reduced. However, this failure of colour discrimination may be so gradual that it is unnoticed by the patient. One of our patients was a market gardener who became somewhat disconcerted by the apparent failure of his apples to ripen. It was only after it was pointed out to him that the apples in his orchard were red and not green did he realize that his appreciation of colour was at fault.

The medicolegal aspect of this colour disturbance is important in that, if a road user or engine driver suffers from tobacco amblyopia, it may not be possible for him to distinguish between green and red traffic lights or railway signals. This loss of colour discrimination was successfully used by defence counsel in a case involving an engine driver who was a heavy pipe-smoker, and who had ignored the danger signal thus causing an accident.

The visual field changes in patients with tobacco amblyopia are characteristic. They consist of a centrocaecal scotoma, usually bilateral though not necessarily equal on the two sides. The scotoma is horizontally oval with a sloping edge and is most easily detected by a reduced stimulus such as a red or small white object. The defect for colour exceeds that for white and there are usually two definite nuclei within the scotoma on the horizontal meridian. An impairment of the temporal colour fields exists within the 30° circle and in more advanced cases a similar defect is also seen to a small white test object[2].

Most cases of tobacco amblyopia improve when smoking is stopped and even when it is reduced. This has obvious disadvantages in that stopping smoking completely is irksome to elderly patients and the recovery rate is variable. Griffith[7] found an average recovery period of 17 months, with extremes of 3 and 42 months, but in 4% of cases the vision continued to deteriorate. It had been suggested that a deficiency of thiamine[8] or other members of the vitamin B group may be a factor, and the response to vitamin B complex and yeast has been studied[9-11] but these clinical trials were not convincing. In 1954 Duke-Elder[12] reported that injecting large doses of cyanocobalamin may cure this condition, but at that time it was not possible to estimate the serum vitamin B_{12} level prior to treatment.

In 1958, we reported the clinical and pathological findings in 13 patients with classical tobacco-amblyopia visual fields[2]. The first patient seen was particularly instructive in that he was a known treated case of pernicious anaemia. At the time of diagnosis he was a lifelong non-smoker and when his haemoglobin was only 4.4 g/dl he had no amblyopia. When we first saw him two years later he had started smoking 16 months previously. His haemoglobin was now 13.8 g/dl but his serum vitamin B_{12} concentration was low at 130 pg/ml, and his visual acuity was 6/60 in each eye and he had tobacco-amblyopia fields. Thus his present degree of vitamin B_{12} deficiency was not sufficient to produce anaemia or evidence of peripheral neuropathy or myelopathy, though he developed severe retrobulbar neuritis soon after starting pipe-smoking.

Three of our patients with tobacco-amblyopia visual fields had serum vitamin B_{12} levels of less than 150 pg/ml. Two non-anaemic patients had histamine-fast achlorhydria and a megaloblastic bone marrow which led to the diagnosis of retrobulbar neuritis in pernicious anaemia. In all 13 patients the effect of parenteral vitamin B_{12} in improving the visual acuity and completely reversing the changes in the visual fields was most encouraging, even if the use of tobacco was continued.

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In 1969, Foulds and associates[13] reported their findings in a larger series of 62 patients in whom tobacco amblyopia was diagnosed by the strict criteria we had adopted. Taking serum vitamin B_{12} levels of below 150 pg/ml as abnormal, 40% had reduced levels, confirming our original findings, and the Schilling test disclosed that 45% had defective vitamin B_{12} absorption.

Retrobulbar neuritis in pernicious anaemia

Our original thesis that retrobulbar neuritis in Addisonian pernicious anaemia could not be solely explained on the basis of vitamin B_{12} deficiency alone was based on a critical review of 31 patients[14]: there was an overwhelming preponderance of males with retrobulbar neuritis (28 cases were men), whereas there is a clear preponderance of females in uncomplicated pernicious anaemia. It was also evident that the development of retrobulbar neuritis was not related to the duration of the disease, the presence or absence of anaemia, or to neurological involvement.

These findings suggested to us that there must be an additional factor to vitamin B_{12} deficiency for the development of retrobulbar neuritis in pernicious anaemia. Evidence was presented that this neurotoxic factor was present in tobacco-smoke, that the overwhelming male incidence was accounted for by pipe-smoking, and that tobacco amblyopia and retrobulbar neuritis in pernicious anaemia and other vitamin B_{12} deficiency disorders are one and the same condition.

Pathogenesis of tobacco amblyopia and retrobulbar neuritis in pernicious anaemia

Tobacco-smoke contains nicotine, carbon monoxide, pyridine and some of its derivatives, namely methyl alcohol, arsenic, lead and cyanide[15]. In a commentary on our findings that in patients with tobacco amblyopia the effect of parenteral vitamin B_{12} in improving the visual acuity and completely reversing the changes in the visual fields was most encouraging, even if the use of tobacco was continued, Wokes[16] indicated that it would be of interest to study the cyanide and thiocyanate metabolism in such patients.

Present methods of measuring free cyanide levels in plasma are inadequate to cope with the small amounts normally circulating. It has been shown that healthy smokers with normal vision have raised plasma cyanocobalamin levels and raised plasma and urinary thiocyanate levels, products of cyanide detoxification, as compared with the levels in healthy non-smokers[17]. Patients with tobacco amblyopia, even if they smoke more than their healthy counterparts, have much lower levels of plasma cyanocobalamin and thiocyanate in their body fluids, indicative of a reduced ability to detoxify the cyanide in the tobacco-smoke to which they are exposed[18].

Thus, clinical and laboratory studies in many centres have confirmed previous opinion that tobacco amblyopia and retrobulbar neuritis in pernicious anaemia are manifestations of chronic cyanide toxicity.

Chronic cyanide neurotoxicity

It is now known that retrobulbar neuritis in pernicious anaemia and other vitamin B_{12} deficiency states may occasionally occur in lifelong non-smokers. Björkenheim[19] found optic neuropathy in 4 of 102 subjectively healthy persons infected with the fish tapeworm, and 3 of these patients with low serum vitamin B_{12} levels were non-smokers. Adams *et al.*[20] reported the finding of optic neuritis in an elderly woman with pernicious anaemia who was a lifelong non-smoker. In this connection, I contend that there may have been exposure to cyanide from some other source than tobacco or an acquired or genetic error of cyanide or vitamin B_{12} metabolism[21,22].

Tropical amblyopia

Besides being present in tobacco-smoke and alcohol, cyanide has a worldwide distribution in the plant kingdom[23]. During the Nigerian 1969 civil war, the incidence of tropical amblyopia and ataxic neuropathy rose sharply among people who fled to the bush and lived on uncooked and unprocessed cassava roots[24,25]. Cassava is the tuber of a manioc which was introduced to Nigeria from South America early this century; now grown as a heavy biannual crop, it is an important source of carbohydrate but contains little protein and is low in sulphur-containing amino acids. Cassava roots are an important staple crop in many tropical countries and contain cyanogenic glycoside, linamarin, from which hydrocyanic acid is released by enzymatic or acid hydrolysis.

If these cassava roots are not peeled and washed and prepared for consumption by roasting or sun-drying, the dietary source of cyanide is high, the deficiency of sulphur-containing amino acids results in a failure to convert ingested cyanide to thiocyanate, and so ophthalmological and neurological complications of chronic cyanide toxicity occur.

Cliff and colleagues have reported cassava-induced paraparesis in a drought stricken area of Mozambique[26], but they failed to mention whether any of those affected had optic neuropathy or visual fields examination. Raised plasma cyanocobalamin levels and raised plasma and urinary thiocyanate levels, products of cyanide detoxification, have been found in Nigerian patients with bilateral optic neuropathy, nerve deafness, myelopathy and sensory ataxia, and in 'West Indian amblyopia' with optic neuropathy and pyramidal tract involvement[25,27]. The visual fields findings are consistent with the strict criteria we adopted in the diagnosis of tobacco-amblyopia fields[2], and add further support to the contention that the dietary source of cyanide contributes to the pathogenesis of tropical amblyopia.

Leber's hereditary optic atrophy

There is still considerable controversy concerning the precise role of cyanide toxicity in the pathogenesis of this disorder, a condition almost solely confined to young males. Its cause is unknown but one hypothesis is that these patients have a defect in cyanide detoxification due to an inborn error of metabolism, resulting in an inability to convert cyanide to thiocyanate by the enzyme thiosulphate sulphur-transferase (rhodanese), which is present in high concentration in the liver[27-29]. Recent work supports this hypothesis in that this enzyme was found to be considerably reduced in the rectal mucosa of subjects with Leber's optic atrophy as compared with healthy controls[30].

Detoxification of cyanide

There are at least three main routes of cyanide detoxification. One mode is by the conversion of

cyanide to thiocyanate by the enzyme thiosulphate sulphurtransferase (rhodanese). It has been postulated that patients with Leber's optic atrophy and possibly dominantly inherited optic atrophy have a genetically determined inability to detoxify cyanide, as present in tobacco-smoke, due to enzyme deficiency. Certainly it is imperative that such patients and relatives at risk should avoid smoking.

A second mode of detoxification is by direct chemical combination of cyanide with sulphur-containing amino acid (di-cysteine) with the formation of 2-aminothiazoline-4-carboxylic acid and cysteine. In tropical and subtropical countries, where protein deficiency and malnutrition is rife, an inadequate supply of sulphur-containing amino acids, essential for cyanide detoxification, may contribute to the pathogenesis of optic neuropathy and sensory ataxia in conditions of high cyanide exposure from a dietary source such as unprocessed cassava roots.

A third mode of cyanide detoxification, both *in vivo* and as a therapeutic agent, is hydroxocobalamin.

Hydroxocobalamin

Evidence from our studies in 1958 indicated that patients with tobacco amblyopia respond to parenteral vitamin B_{12} therapy even if they continue smoking against advice[2]. It is important to recall that the only preparation of vitamin B_{12} then available for our therapeutic use was manufactured under the trade name Cytamen. Cytamen was not 100% pure cyanocobalamin, as it is now, but contained varying proportions of hydroxocobalamin, possibly as high as 30%, due to impurity of manufacture and to the action of photolysis in converting cyanocobalamin to hydroxocobalamin. It is hydroxocobalamin, not cyanocobalamin, which is a potent cyanide antagonist: raised plasma cyanocobalamin levels and raised plasma and urinary thiocyanate levels are products of cyanide detoxification.

Patients with tobacco amblyopia who have normal serum vitamin B_{12} levels need not continue treatment with hydroxocobalamin after their visual acuity and visual fields have returned to normal, providing they abstain from further smoking. Those with low serum vitamin B_{12} levels and evidence of defective vitamin B_{12} absorption will need to continue indefinitely with hydroxocobalamin irrespective of their smoking habits, as will patients with pernicious anaemia who are at risk of developing optic neuropathy if they are smokers.

The therapeutic value of either parenteral hydroxocobalamin or oral di-cysteine (cystine) or a combination of each in Leber's optic atrophy is not proven[31]. Nikoskelainen and colleagues[32] stated that hydroxocobalamin does not reverse or halt serious impairment of vision. As a result of the development and application of the chromato-bioautographic method of estimating individual plasmacobalamins[27] it may in future be possible to identify patients at risk in genetically determined disorders, such as Leber's optic atrophy, and thus initiate effective early prophylactic measures such as stopping smoking and hydroxocobalamin before the onset of irreversible visual failure.

Because confusion persists among doctors over the various commercial forms of vitamin B_{12} available for therapeutic use and about their possible adverse effects in neuro-ophthalmological disorders, we presented a case for withdrawal of cyanocobalamin in favour of hydroxocobalamin and submitted this in 1970 to the Committee on Safety of Medicines[33]. As no action was taken by the manufacturers, we asked in 1978 'why has cyanocobalamin not been withdrawn?'. We laid particular emphasis on the fact that hydroxocobalamin, but not cyanocobalamin, was a powerful cyanide antagonist. Some patients with tobacco amblyopia fail to respond to treatment because, although hydroxocobalamin has been prescribed, cyanocobalamin has been administered instead. The diagnosis may then be questioned, treatment stopped and the patient condemned to a life of poor sight[34].

Our concern over the misuse of cyanocobalamin received some support: Linnell and co-workers stated that there was no condition in which it had been claimed that cyanocobalamin was preferable to hydroxocobalamin and that there was no place for its continued use[35]. Yet the World Health Organization's committee on the selection of essential drugs lists only cyanocobalamin, thus placing an incalculable number of patients with tobacco and nutritional amblyopia and optic neuropathy in pernicious anaemia at risk[36].

In 1981, the Committee on Safety of Medicines drew attention to our thesis that hydroxocobalamin is effective in the treatment of certain optic neuropathies, of which tobacco amblyopia is an example, but cyanocobalamin is not[37]. Since tobacco amblyopia occasionally occurs in pernicious anaemia, it is clearly preferable to use hydroxocobalamin routinely instead of cyanocobalamin. Despite all these recommendations, certain manufacturers[38] still have not withdrawn cyanocobalamin in favour of hydroxocobalamin for therapeutic use.

Discussion

Since our original work on the aetiology of tobacco amblyopia and retrobulbar neuritis in pernicious anaemia some 30 years ago, clinical and laboratory studies on the pathogenesis of deficiency diseases and degenerative neuropathies have been continued in many centres. The precise role of chronic cyanide intoxication has merited particular attention and current concepts in our knowledge of cyanide and vitamin B_{12} metabolism have been presented.

Optic neuropathy, often associated with sensory ataxia and pyramidal tract involvement, is particularly prone to occur in tropical and subtropical countries where nutrition is poor and the indigenous population suffers from a low protein and sulphur-containing amino acid intake and high cyanide exposure from a dietary source such as unprocessed cassava roots.

Particular attention has been drawn to the fact that hydroxocobalamin, but not cyanocobalamin, is a powerful cyanide antagonist. In the Western hemisphere, tobacco amblyopia and optic neuropathy in pernicious anaemia and other vitamin B_{12} deficiency disorders is due to failure to detoxify cyanide, as present in tobacco-smoke, by hydroxocobalamin. I consider that if the indiscriminate dumping of industrial cyanide waste continues unchecked, with the inherent risk of pollution of food and water supplies, there may well come a time when more widespread chronic cyanide neurotoxicity occurs from a dietary source in persons with a genetic or acquired error of cyanide or vitamin B_{12} metabolism[39].

It has been postulated that Leber's hereditary optic atrophy is due to a genetically determined inability to detoxify cyanide, as present in tobacco-smoke, due to a deficiency of the enzyme thiosulphate sulphurtransferase (rhodanese), normally present in high concentration in the liver.

Some patients with tobacco amblyopia fail to respond to treatment because they have received cyanocobalamin rather than the hydroxocobalamin prescribed. The retention of cyanocobalamin for therapeutic use and its selection places an incalculable number of patients with tropical and tobacco amblyopia and optic neuropathy in pernicious anaemia at risk of permanent blindness.

Looking to the future, it is possible that other cyanide antagonists, with the obvious advantage of oral administration, will become available. I have strongly urged that all patients with tobacco and nutritional amblyopia, and optic neuropathy, myelopathy or neuropathy of obscure origin, should be very carefully screened for evidence of vitamin B_{12} deficiency before embarking on any therapy other than hydroxocobalamin[40].

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