OPTIC ATROPHY INDUCED BY CHLORAMPHENICOL*

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CHLORAMPHENICOL is an antibiotic that is used mainly for treating diseases caused by bacteria which are not sensitive to other, less toxic, antibiotics. Some of these diseases entail prolonged courses of treatment and the drug has to be administered for months or even years; the commonest diseases requiring prolonged treatment are subacute bacterial endocarditis, pyelonephritis, and fibrocystic disease of the pancreas. Haematological investigations are carried out periodically because of the danger of agranulocytosis and aplastic anaemia.

A number of reports has now been received of optic neuritis occurring during chloramphenicol therapy. A further case is described below.

Case Report

A girl born on February 22, 1958, of white parents was seen in May, 1959, because of recurrent chest infection. A diagnosis of fibrocystic disease of the pancreas was made, and she was treated with continuous antibiotic therapy from January, 1959, starting with erythromycin, 750 mg. daily, increasing to 1 g. daily in September, 1959 (Figure). Terramycin, 750 mg. daily, was given for one

FIGURE.—Dosage of antibiotics January, 1959, to August, 1962.

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week in January, 1959. During the whole course of treatment she received oral Pancrex (pancreatic extract), liver extract, and vitamin emulsion, 1 drachm twice daily, made up as follows:

Thiamine HCl	4 mg.	} in 1. drachm
Riboflavin	4 mg.	
Nicotinamide	20 mg.	
Pyridoxin	0.4 mg.	
Pantothenic acid	4 mg.	
Folic acid	0.5 mg.	
Ascorbic acid	25 mg.	
Vitamin A	15,000 units	}
Vitamin D	3,000 units	

Neomycin aerosol 1 g. four times daily was also given in addition from January, 1959. This method of administering the drug produces a high concentration at the site at which it is required without having high serological levels that would otherwise be necessary with systemic administration. Neomycin is liable to cause deafness if given systemically. In January and April, 1960, Albamycin was introduced to replace the erythromycin, but it was withdrawn rapidly each time, because of an allergic rash. In May, 1961, chloramphenicol, 1 g. daily, replaced the erythromycin because of bacterial insensitivity and worsening of the general condition. This was used in conjunction with the Neomycin aerosol until July, when Celbenin aerosol was added. In October, 1961, a lingectomy and apicectomy of the left lung was performed.

In December, 1961, Celbenin and streptomycin aerosol were given, but this was replaced with Neomycin. She continued with this treatment until May, 1962.

In February, 1962, she had been noted in the ward to be peering at objects. She was then examined in the Eye Department, where she was found to have a divergent squint.

Orthoptic Report (April, 1962): Constant left divergent squint. Visual acuity (Hand test), right 6/60, left 6/60, but doubtful. "At less than 2/18 she completely loses interest and guesses haphazardly—unless allowed to hold it 7" away from face and then very cooperative to the smallest 6/6 picture".

The fundi were normal and not myopic.

In June, 1962, the mother reported that the child was worse. The binocular visual acuity was 4/9 (Hand test), but her answers were very variable. It was thought that the child could see fairly well and that the symptoms might have been due to an emotional disorder. The fundi were still completely normal. She was seen again in August, 1962, because her vision had obviously become poor, and she was found to have bilateral primary optic atrophy. The visual acuity was found to be 1/60 right and left. She was given large doses of vitamin B complex and B₁₂ injections but very little improvement occurred, and the vision has remained approximately constant since then at 1/36, right and left.

Previous Cases

Eight cases of optic neuritis presumed to have been caused by chloramphenicol therapy have been reported in the literature. All these patients had received large amounts of the drug for severe illnesses not responding to other drugs. One further case has been briefly noted (Denning, Bruce, and Spalter, 1963). These cases are briefly summarized below.

(1) Gewin and Friou (1951): A man aged 22 years with subacute bacterial endocarditis caused by *Staphylococcus aureus* was treated for 66 days, until he had received a total of 190 g. chloramphenicol, after which he developed yellow vision and was found to have papilloedema. He also had numbness and tingling in both feet, nausea, vomiting, hepatitis, and an oral rash. The drug was discontinued, and he was treated with vitamins A, B, C, D, and B₁₂. The visual acuity returned to normal in 39 days, and the peripheral neuritis lasted a further 2 weeks. He had also received chlortetracycline for part of the time.

(2) Wallenstein and Snyder (1952): A 24-year-old female with ulcerative colitis and an abscess of the buttock was treated for 171 days until she had received a total of 427 g. chloramphenicol. She was receiving vitamins concurrently. The visual acuity dropped to 20/2000, she developed granulocytopenia and peripheral neuritis, and was found to have optic neuritis with swollen optic discs. The chloramphenicol was stopped and she was given extra vitamin B complex. The vision returned to normal within 6 weeks and the peripheral neuritis stopped after 8 weeks.

(3) Lasky, Pincus, and Katlan (1953): A boy aged 14 with subacute bacterial endocarditis suddenly became blind after treatment for 42 days with chloramphenicol (total 252 g.). He was found to have fixed, dilated pupils, pale oedematous discs, and retinal haemorrhages, and was also anaemic. The drug was discontinued, but the visual acuity in the right eye improved only to counting figures and in the left to 6/60.

(4) Cole, Cole, and Janoff (1957): A man aged 44 with subacute bacterial endocarditis was treated for 199 days with a total of 323 g. chloramphenicol, having previously received penicillin and streptomycin. His vision became blurred, and he was found to have swollen optic discs and constricted visual fields but the drug was continued for 3 more weeks. He was treated with thiamin, vitamin B₁₂, and acetazolamide. The visual acuity returned to normal 30 days after the chloramphenicol was stopped.

(5) Prevatt and Hunt (1957): A 32-year-old man with chronic meliodosis received more than 1,600 g. chloramphenicol during a period of 22 months. He had also received ACTH, penicillin, and chlortetracycline. He had three episodes of smoky vision, though the eyes appeared normal. The drug was stopped and the symptoms did not recur.

(6) Joy, Scalettar, and Sodee (1960): A man aged 20 with chronic meliodosis was treated for 144 days with a total of 422 g. chloramphenicol and had also received novobiocin and sulph-suxazole. He developed blurred vision and was found to have papilloedema and constricted visual fields, and also peripheral neuritis and neutropaenia. The chloramphenicol was given for 2 more weeks after the onset of these symptoms. He was treated with vitamin B complex, B₁₂, and pyridoxin. The vision returned to normal in 63 days, but the peripheral neuritis persisted.

(7) Wilson (1962): A woman aged 37 with chronic pyelonephritis was treated for 9 months with a total of approximately 200 g. chloramphenicol; she also received streptomycin for 3 months, but this was stopped because of tinnitus. She developed blurring of vision and the visual acuity fell from 6/9 in each eye to 6/36 in the right, 6/24 in the left, in the course of one month. Peripheral neuritis also developed. She was treated with vitamin B complex and the visual acuity improved to 6/18 and 6/12. The drug was then stopped and the visual acuity further improved to 6/5 in the right eye and 6/6 in the left.

(8) Wilson (1962): A woman aged 31 with chronic pyelonephritis was given chloramphenicol over 10 months, when she developed poor vision and peripheral neuritis. The fundi showed only slight myopic changes and slight pallor of the optic discs, but the visual acuity was reduced to 1/60 in each eye. The chloramphenicol was discontinued, and she was treated with vitamin B complex, but the visual acuity improved only slightly to 2/60 in the right eye and 2/24 in the left. The patient died 3 months later.

A further case is that mentioned by Dinning and others (1963) of a child with fibrocystic disease of the pancreas treated with chloramphenicol, who developed optic neuritis.

Discussion

Wilson (1962) pointed out that many of the features of chloramphenicol toxicity resemble those described as nutritional neuropathy and amblyopia, such as were seen after the last war in the Far East, particularly in prisoners of war. No specific deficiency was discovered, but the condition was believed to be due mainly to lack of vitamins of the B group.

Case 6 improved on vitamin therapy while he was still receiving chloramphenicol. Case 2 was receiving vitamins throughout treatment, but she was suffering from ulcerative colitis which may have interfered with vitamin absorption. Case 8 and my own case reported above were both receiving vitamins throughout treatment, but both developed severe visual loss before any fundus changes were visible. In my case optic atrophy developed subsequently, whereas Case 8 showed no definite fundus abnormality up to the time of her death. It is possible that long-term chloramphenicol therapy causes a vitamin deficiency or block which is manifested

by both optic and peripheral neuritis. The optic neuritis may present as loss of vision, with or without papilloedema; the swelling of the disc may be an attribute either of the acuteness of the condition or of the site of the lesion. If the nerve is affected behind the eye no swelling will appear, or if vitamin therapy minimizes the deficiency over a long period of time the lesion may not be large enough to cause oedema of the nerve head. Case 8 received chloramphenicol for 2 months and my case for 6 months after the onset of visual symptoms, and neither showed any significant recovery. (Case 3 also showed very little improvement in vision, but this may have been due to the retinal haemorrhages.)

The severity of the visual defect and the failure of recovery of these two patients are most probably due to the continuation of chloramphenicol therapy after the onset of symptoms, but may be due to an aggravation of a specific vitamin deficiency by the administration of the other vitamins, such as used to occur in the treatment of pernicious anaemia with folic acid. This may also be a factor in the production of papilloedema, except in Case 5 who had a very slight visual disturbance and no papilloedema.

It is not known whether the chloramphenicol acts on the ganglion cells of the retina or on the optic nerve itself. The parents of the patient whose case is reported declined to have an electroretinogram performed, which might have helped in locating the defect. An alternative cause may be a direct toxic action of the drug on the optic and peripheral nerves. The most common toxic effects of chloramphenicol are aplastic anaemia, granulocytopenia, and thrombocytopenic purpura. The drug is one of the nitrobenzene compounds which are recognized as depressors of bone marrow, and this effect may be produced by interference with some of the vitamins of the B group, thus causing a disturbance of carbohydrate metabolism (Martindale, 1952; Sollman, 1957).

The only drug common to this group of patients is chloramphenicol. My patient was receiving many other drugs, *viz.* oral Pancrex, vitamins, liver extract, and aerosol Celbenin and Neomycin, but there are no reports of toxicity to the eye from these drugs. The serum levels of Neomycin are low when it is administered by aerosol, though some cases of ototoxicity have been reported.

The difficulties in diagnosis in this case were due to the age of the child and the absence of physical signs in the fundus.

Summary

A case of bilateral optic neuritis in a child aged 4 being treated with chloramphenicol for bronchiectasis and fibrocystic disease of the pancreas is described. The literature is reviewed and the mechanism of the effect is discussed.

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