Thioridazine (Melleril) retinopathy

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The drug thioridazine was first introduced in 1959, and Weekley, Potts, Reboton, and May (1960) reported the first cases of pigmentary retinopathy, in four patients who had been given approximately 2 g. daily for 30–50 days. The manufacturers (Sandoz) subsequently recommended that a daily dose of 800 mg. should not be exceeded and since then only about half a dozen articles have appeared (all in American publications) relating to this condition. We have been unable to find any cases of thioridazine-induced retinopathy reported from Europe or England. The following is the first case to be reported from Australia and it is illustrated for the first time by a fluorescein fundus photograph.

Case report

A 24-year-old male schizophrenic had had five periods of hospitalization since 1961 for florid symptoms of his illness. Each episode was controlled by the use of thioridazine (Melleril) and electroconvulsive therapy (ECT). To maintain remission, it had been necessary to raise the daily maintenance dose of Melleril after each episode, from 200 mg. daily in 1961 to 800 mg. daily since 1967. In March, 1970, he developed acute symptoms of thought disorder, elevated incongruous mood, delusions, and hyperactivity, and these were treated initially with a combination of Melleril and haloperidol (Serenace) in the Day Hospital, but without success. After an emergency admission because of violent behaviour, daily ECT was instituted and the daily dosage of Melleril was increased until control of symptoms was finally achieved after six ECTs and a massive daily dosage of 2,800 mg. Melleril. During the next month three further ECTs were necessary to maintain this remission, and he was finally well enough to be discharged on the maintenance dosage of 2,800 mg. Melleril. This was reduced after 1 week as an outpatient to 1,800 mg. daily. The onset of visual symptoms began one week later.

The patient had always responded well to the combination of ECT and Melleril and had shown no side-effects in 9 years of Melleril treatment, including 3 years on the maximum recommended dosage. An early attempt to combine his usual phenothiazine with haloperidol had failed to control the development of his acute symptoms. Rather than risk the problems of multiple pharmacology in high dosages, it was decided to restrict treatment to the intensive use of ECT and a well-known and well-tolerated phenothiazine in massive dosage. Subsequent to the development of his visual symptoms, the Melleril dosage was reduced and then stopped and trifluoperazine (Stelazine) was substituted in dosages of 80 mg. daily. This failed to maintain his remission and hospitalization for further ECT was necessary. At present time (February, 1971) no satisfactory remission of symptoms has yet been achieved. The current daily dosage of drugs is of the order of 400 mg. Melleril and 10 mg. Stelazine, but mood fluctuation in particular has prevented him from leaving hospital.

Ophthalmological examination

The patient was required in his job to select and pack motor spare-parts but complained that they had dark patches over them. This made selection difficult and he had to grope about, taking much longer than normal. Objects appeared darker than normal. He could recognize his sister if she stood in bright sunlight but not in the lounge in subdued light.

He was first examined on June 9, 1970. The uncorrected visual acuity was right 6/12, J1 part,; left 6/12, J1. It could be corrected to 6/6 but not to 6/5, with -1 D sph., -0.25 D cyl., axis 180° in both eyes.

No abnormality could be seen in the cornea or lens with the high-power slit lamp. The discs, bloodvessels, maculae, and fundi generally appeared normal ophthalmoscopically. There was, however, a marked visual field loss in each eye corresponding roughly to a ring scotoma from 3 to 15° (Fig. 1).

FIG. 1 Central fields (2/1000 white) showing roughly a ring scotoma between 3 and 15°

The thioridazine was stopped, but a week later there was no change in the symptoms or findings. The macular areas in particular looked quite normal. On June 19, 1970, *i.e.* 10 days after ceasing thioridazine, a fine granular pigmentation could be seen at the macular areas. In the fundus photographs of June 19, a diffuse peppery perimacular pigmentation can be seen. The pigment is seen to consist of small black discrete round spots scattered fairly uniformly around the macula.

In the right fundus, just above and lateral to the macula (Fig. 2), there is a horseshoe-shaped yellow area (arrowed), contained between two descending branches of an arteriole. This area is thought to be exudative in nature. Three smaller white areas are also seen, two above in the forks of two arterioles and one below closely related to the lower wall of a horizontally-running arteriole. These are light reflex artefacts. The left fundus showed a similar pigmentary retinopathy.

Fluorescein angiography not only shows all the pigment areas seen previously but also reveals many more that were unsuspected, outlined against the choroidal fluorescence. In the right fundus, for instance (Fig. 3), above and lateral to the macula where our attention was concentrated previously, there can now be seen a large conglomeration of pigment. The yellow area can no longer be seen, being presumably transparent to the emission wavelength of fluorescein ($5,200$ – $5,300$ Å). The yellow area and the patch of pigment do not coincide. Since this pigment patch was not seen in the fundus photograph it must be posterior to the pigment epithelium. It would thus appear that the pigment is distributed not only in the outer layers of the retina, but also sub-retinally. It is not known what the yellow area represents. Both the pigment and the yellow 'exudate' had greatly diminished 4 months later. The diminution in pigmentation was accompanied by a disappearance of the scotoma and a return of the visual acuity to normal. Thus, on October 29, 1970, the central fields were full to 2/1,000 white and the refraction was right -0.75 D sph. = $6/4$ –1; left -0.75 D cyl. = $6/4$ –1. The patient said the dark areas in his field of vision disappeared about one week after ceasing Melleril and he states that his vision now is as good as ever it was.

FIG. 2 Right fundus photograph (June 19, 1970), showing mainly perimacular peppery pigmentation. There is a yellow horseshoe-shaped area just above and lateral to the macula contained within two descending arterioles. This exudate is apparently anterior to a third arteriole passing downwards between the other two. Two other small white 'exudates' can be seen in the forks of the medial two arterioles above and there is one small area below. These last three appearances are light reflex artefacts

FIG. 3 Fluorescein angiogram of right fundus 14 seconds after injection (July 16, 1970). A large aggregation of pigment is seen above and lateral to the macula. It is not visible in the corresponding fundus photograph and does not coincide with the yellow horseshoe area seen in Fig. 2

A right fluorescein angiogram was repeated on October 29, 1970, for comparison with that done in June, 1970, but technically was not very successful. However, enough can be seen (Fig. 4) to confirm the overall decrease in pigmentation. No vascular abnormality or leakage of fluorescein could be seen in any of the fluorescein photographs.

FIG. 4 Right fluorescein angiogram 7 minutes after injection (October 29, 1970). There is a general decrease in perimacular pigmentation compared with that seen 3½ months previously

Discussion

Pigmentary retinopathy due to Melleril (thioridazine) has been reported only in patients receiving greater doses than the recommended maximum of 800 mg. per day (Sandoz). Generally the daily level has to be above 1 g. and the length of treatment 20 to 50 days, before retinopathy appears. An interesting point is the occurrence of subjective symptoms a week or so before any signs are ophthalmoscopically visible in the fundi. Vision may remain permanently depressed, but in the case reported here, the visual fields and visual acuity returned to normal after prompt cessation of the drug, even though pigmentation was still visible. None of the authors has seen a chlorpromazine retinopathy and it is now generally believed that it can only occur with piperidine-substituted compounds such as Melleril.

Summary

A case of pigmentary retinopathy due to high dosage with Melleril is described. A yellow substance hitherto unreported is shown to occur in association with the pigment. After the drug was stopped the vision improved and concurrently the pigmentation decreased. Fluorescein angiography, reported here for the first time, shows the amount of pigment to be much greater than that observed ophthalmoscopically. It also shows that large amounts are located subretinally.

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Reference

WEEKLEY, R. D., A. M., REBOTON, J., and MAY, R. H. (1960) *Arch. Ophthalm. (Chicago)*, **64**, 65