Drug Intoxication and Neurological Episodes in Chronic Renal Failure

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British Medical Journal, 1970, 2, 394-395

Summary: Of 178 episodes of neurological derangement in 103 patients with renal failure, only about 40% were due to known causes such as hypertension or electrolyte failure. One-third were due to drug intoxication and no definite aetiology was found for the remainder. Drug intoxication is due partly to the accumulation of a drug normally excreted by the kidney and partly to a greater susceptibility of the central nervous system in uraemic patients. The prognosis is favourable.

Introduction

Neuropsychiatric features in chronic renal failure may be due to many causes. The best known is hypertension producing a cerebrovascular accident, but abnormalities of fluid and electrolyte metabolism may also account for some neurological conditions (Hamburger and Mathé, 1952). Nevertheless, these two factors can explain only 30 to 40% of the neurological problems observed. Though some cases remain unexplained, we have been struck by the frequent history of drug intoxication in the days preceding the neurological episodes (Richet, Fabre, de Freudenreich, and Podevin, 1966; Richet and Vachon, 1966). This possibility is not even considered in recent reviews (Tyler, 1968), and we have therefore reviewed our experience of the incidence and clinical aspects of neuropsychiatric episodes attributable to drugs in patients with chronic renal failure.

Patients

A total of 103 patients presenting 178 neuropsychiatric episodes between 1963 and 1968 were reviewed. All had renal failure and the blood urea was always above 60 mg./100 ml., and in most cases above 100 mg./100 ml. (Table I). The duration of renal failure was known in 88 patients, being less than three years in 30, between 3 and 10 years in 29, and more than 10 years in 29. The aetiology of the various nephropathies is shown in Table II, and the clinical symptoms of the 178 psychiatric manifestations in Table III. Only major manifestations were included in the present survey, and minor symptoms such as cramps, muscular twitching, and headaches were excluded.

Results

There are five main causes for the 178 episodes: cerebrovascular accidents due to hypertension (42 cases with

TABLE I.—Blood Urea Levels in 162 Cases of Neurological Episodes in Chronic Renal Failure

Blood urea (mg./100 ml.)	60-100	100-200	200-300	300-400	>400
No. of accidents	17	64	36	25	20

TABLE II.—Aetiology of 103 Nephropathies					
Interstitial nephropathies	..	..	..	..	38
Polycystic kidneys	..	..	..	..	10
Glomerular nephropathies	..	..	..	..	17
Amyloidosis	..	..	..	..	3
Nephrosclerosis	..	..	..	..	14
Unclassified	..	..	..	..	21

TABLE III.—Clinical Symptoms in 178 Neurological Episodes of Chronic Renal Failure

Psychic disturbances	..	..	..	..	50
Seizures	..	..	..	..	40
Focal cerebral diseases	..	..	..	..	34
Light coma	..	..	..	..	18
VIII nerve	..	..	..	..	11
Paresthesias	..	..	..	..	8
Peripheral nerve palsy	..	..	..	..	5
Extrapyramidal syndrome	..	..	..	..	5
Oculomotor syndromes	..	..	..	..	4

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the poorest outcome, 14 deaths); primary neurological disease (17 cases, 3 deaths); disturbances of the electrolyte or acid-base balance (11 cases), in which the prognosis was favourable, all patients spontaneously recovering in two or three days; drug intoxication (50 cases, 4 deaths); and unclassified causes (58 cases, 15 deaths).

Because of minor restlessness, this man aged 46 was put on long-acting barbiturates by his family doctor. Because he showed no improvement, the dosage was progressively increased, and on admission to hospital he was confused and agitated—a state which lasted 11 days despite the cessation of all drug therapy. Peritoneal dialysis was then instituted, and removed 700 mg. of barbiturates. The mental state improved progressively afterwards.

The first three groups are well recognized causes. The fourth group comprised drug intoxications, 50 incidents being attributed to this cause after another known cause had been excluded. Cases were not included in this category unless they satisfied the following two criteria; firstly, that the features were known to occur after intoxication with the particular drug, and, secondly, that the features showed definite regression once the drug was withdrawn. Another 11 cases have been added to this group in which drug intoxication could be strongly suspected but was also associated with another possible aetiology. The drugs involved (Table IV) included mainly antibiotics and sedatives.

TABLE IV.—Drugs Responsible for 61 Cases of Neurological Accidents of Chronic Renal Failure

Drug	No. of Cases	Severity
Colistin	9	+++
Streptomycin	4	+++
Kanamycin	1	+++
Barbiturates	8	+++
Penicillin	6	+++
Haloperidol	3	?
Piperazine	3	++
Insulin	2	++
Corticoids	2	±
Methoserpidine	1	±
Pentolinium	1	±
Heparin	1	±
Promethazine	1	±
Isoniazid	2	++
Atropine	2	++
Combined drugs	4	++
Definite drug intoxication	50 cases	
Isoniazid	3	++
Para-aminosalicylic acid	1	+++
Streptomycin	1	+++
Diphenylhydantoin	1	++
Curare	1	+++
Promethazine	1	+
Corticosteroids	2	±
Penicillin	1	+++
Probable drug intoxication	11 cases	

A sequence often encountered in the history of these episodes was that because of minor symptoms (such as nausea or insomnia) the patient took sedatives. These then gave rise to mental disturbances for which new drugs were given at a higher dosage. In their turn the latter themselves created new features, for which new drugs were prescribed, therefore setting up a vicious circle. The predominant clinical symptoms were in most cases various psychic disturbances (Table V).

TABLE V.—Clinical Picture of 50 Neuropsychic Accidents Attributed to Drug Intoxication

Psychic disturbances	24
Cerebral haemorrhage (anticoagulant therapy)	3
Seizures	6
Light coma	4
Extrapyramidal syndrome	5
VIII nerve	8

Clinically obvious extrapyramidal syndromes were found in only five cases. Among the other cases, however, single extrapyramidal signs were frequently seen—for example, cog-wheel rigidity or akinetic aspect of the face. The prognosis of this type of disorder is good, since only 6 of 61 patients died. Complete regression occurred in 48 cases after simple withdrawal of the drug. Seven patients were left with definitive sequelae such as deafness due to streptomycin (six cases) and polyneuritis after isoniazid (one case).

The fifth and last group comprised unclassified causes, in which there were 58 cases. Of these, 11 have been included in the preceding group because of a strong suspicion of drug intoxication. No definite cause could be found for the 47 remaining cases. Thirty-seven occurred in patients with very severe renal failure, characteristically having blood urea levels over 200 mg./100 ml. as well as hypocalcaemia, hyponatraemia, and hypertension. The last 10 episodes occurred in patients with only moderately severe renal failure, and in them the abnormal neurological features were probably related to other causes such as essential epilepsy or alcoholic neuropathy.

Discussion

Our findings show that only about 40% of the neurological episodes seen in patients with renal failure can be explained by known causes such as hypertension, disorders of electrolyte metabolism, and so-called "separate neurological state." About one-third are probably due to drug intoxication, and no definite aetiology can be found for the remainder.

The simplest mechanism for drug intolerance in uraemia is obviously accumulation of a substance which is normally excreted in an active form via the kidney. This can be easily measured by comparing the half-life of a drug in the serum of normal people with that in patients with chronic renal failure. Nevertheless, incidents due to drug intolerance may occur in uraemia in the absence of any abnormal retention. This is well known for thiopentone (Dundee and Richards, 1954), and colistin (Lissac, Amiel, Morel-Maroger, and Mignon, 1964; Richet, Ardaillou, and Sultan, 1962). Half the normal intravenous dose of thiopentone is necessary to induce anaesthesia in patients with chronic renal failure when compared with normal. Obviously in such a short time renal excretion cannot play any part. Similarly, colistin (which is mainly excreted by the kidney) produces effects which cannot be explained by accumulation only. Indeed, this antibiotic is a frequent cause of neurological episodes in chronic renal failure, whereas it is much better tolerated in acute renal failure. Furthermore, given in high dosage to normal people it produces renal lesions before neurological symptoms appear, whereas in chronic renal failure neurological symptoms occur without any sign of nephrotoxicity.

These observations cannot be explained on the basis of accumulation alone, and imply a greater susceptibility of the central nervous system in uraemia. Though hard to define this conception agrees well with several observations. Firstly, there is the presence of decreased cerebral metabolism, as indicated by abnormal slow waves on the E.E.G. (Lossky-Nekhorocheff, Lérique-Koechlin, Funck-Brentano, and Delprat, 1959) and decreased oxygen consumption by the brain (Heyman, Patterson, and Jones, 1951). Secondly, as Olsen (1961) has shown, these patients may have various lesions of the central nervous system, which may be the anatomical counterpart of the disturbed cerebral metabolism. Moreover, Jennekens (1969) has shown the existence of diffuse segmental demyelination as well as Wallerian degeneration, both of these lesions indicating increased susceptibility of the peripheral nervous system (Jebsen, Tenckhoff, and Honet, 1967; Tenckhoff, Baen, Jebsen, and Spiegler, 1965). Thirdly, and perhaps most importantly, the permeability of the meninges is increased. This was first suggested by Baur (1932) and more recently by Freeman, Sheff, Maher, and Schreiner (1962), who showed that meningeal permeability to bromine was increased in both acute and chronic renal failure.

All these findings support the suggestion that the neuropsychiatric abnormalities seen in patients with chronic renal failure are due to "endogenous uraemic toxins" gaining access to an already damaged central nervous system (Sharp and Murphy, 1964; Teschan, Murphy, and Sharp, 1964). This theory could well account for some of our "unclassified" cases, and again could explain the drug intolerance shown by some patients by postulating a similar increased permeability of the meninges to substances used in treatment.

Since as high a proportion as one-third of the neuropsychiatric disorders occurring in chronic renal failure may be due to drug intoxication, this aetiology must always be considered in these cases. In the absence of any biochemical proof complete regression of symptoms after withdrawal of all drugs for three days is the best clinical argument supporting this type of incident. Nevertheless, if no improvement occurs after such a trial and there is still a strong suspicion of drug intoxication, dialysis should be carried out and may bring about striking improvement as well as proof of the diagnosis (see Chart). Treatment should also be prophylactic, by using only essential drugs and by bearing in mind the metabolism of various drugs in chronic renal failure (Kunin, 1967; Reubi, 1967).

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