Neurologic Complications in Diabetics after Metrizamide Lumbar Myelography

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Recognized risk factors for metrizamide myelography are seizure disorder, seizure-threshold-lowering drugs, dehydration, and possibly age. After observing serious neurologic complications in diabetic patients after routine metrizamide myelography, a retrospective study was conducted to determine if diabetes should be considered another independent and important risk factor. Forty-one diabetic patients who had lumbar metrizamide myelograms were compared with a control group of 110 nondiabetic patients. A significantly higher incidence was found of severe vomiting (15% vs. 3%, $p < 0.01$) and neurologic complications (20% vs. 2%, $p < 0.001$) in the diabetic population. Neurologic complications included one case each of seizure, severe encephalopathy, auditory and visual hallucinations, and prolonged somnolence and four cases of confusion-anxiety. Four of the diabetic patients had major transient elevations of blood pressure. These findings suggest that diabetics are a high-risk population for metrizamide myelography. The dose of metrizamide should be minimized, whenever possible. The new nonionic myelographic agents may prove to be safer in this population, but caution and careful follow-up should be exercised in the initial trials with these patients.

Although metrizamide is less neurotoxic than ionic, water-soluble contrast agents, there continue to be reports of rare but serious adverse reactions after myelography. These include seizure, encephalopathy, and neuropsychiatric abnormalities [1–6].

Complications from metrizamide are often dose-related, resulting from excessive intracranial concentrations of the drug [7–12]. However, high-risk factors independent of dose have been described. These include a seizure history, drugs that lower the seizure threshold, and dehydration [1, 4].

Patients with diabetes mellitus have not previously been considered a high-risk population for metrizamide myelography. However, after observing serious neurologic complications in diabetic patients after lumbar myelography with metrizamide, we conducted a retrospective study to determine if diabetes should be considered another independent and important risk factor.

Materials and Methods

We reviewed the records of 41 diabetic patients who underwent lumbar metrizamide myelography at the University of Rochester Medical Center from 1979 through 1983. The control group was composed of 110 randomly selected nondiabetic patients studied during the same period.

In our study a patient was considered diabetic only when the disease was diagnosed by a physician and some form of medical or dietary treatment was prescribed. Specifically excluded from both groups were cases of questionable diabetes; patients who had cervical, thoracic, or multilevel examinations; and patients studied with Pantopaque or other water-soluble agents. Twenty-one patients were insulin-dependent, 16 were treated with oral medication, and four were controlled by diet.

Symptoms and signs such as headache, nausea, and vomiting were classified into major

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categories based on physician and nursing notes. The guideline for each category was determined before chart review. For example, vomiting was defined as mild for the purpose of this study if there were one or few episodes; moderate if there were multiple episodes over many hours; and severe if debilitating and prolonged over 24 hr and not relieved by medication.

Since the neuropsychiatric syndrome (confusion, memory deficit, agitation) was not specifically tested for, and since symptoms are frequently subclinical, our results probably underestimate its frequency [5, 6, 13]. Cases in which the patient was described as irritable were attributed to discomfort rather than drug effect unless specific assessments were made by the patient's physician. Consequently, milder anxiety reactions and irritability are underestimated by study design.

Neurologic symptoms were attributed to drug effect rather than diabetes (hypoglycemia) only if there was no documentation of probable or possible hypoglycemia, no evidence for a postictal reaction, and if the complication was prolonged over 6 hr.

Because of the high incidence of low back pain and urinary retention in the study population before myelography and the difficulty in assessing postmyelogram changes in these symptoms, these complications were not included in this study.

Statistical analysis was by Chi-square test. p values are not reported when 20% of the cells contained fewer than five patients.

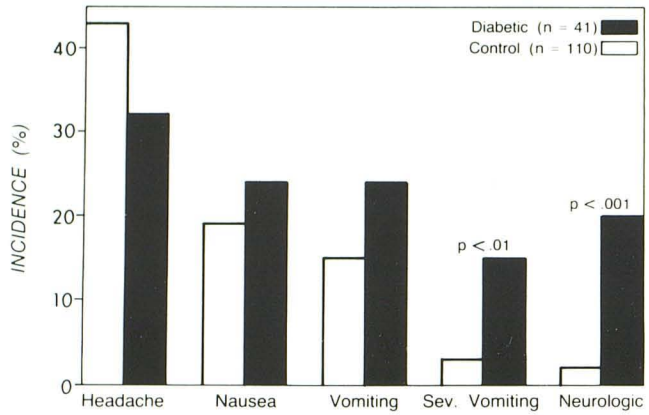

Fig. 1.—Complications in all patients.

Results

The incidence of the most frequent complications are shown in figure 1. Except for headache, for which the control group showed a slightly greater rate of occurrence, all adverse reactions and complications were more frequent in the diabetic patients. The incidence of vomiting was 24% in the diabetics and 15% in the controls. A significant difference was noted in the incidence of severe vomiting lasting longer than 24 hr. This occurred in 15% of the diabetic patients, five times more frequent than in the controls ($p < 0.01$). Overall, neurologic complications occurred in 20% of the diabetic patients, 10 times more frequent than in the controls ($p < 0.001$).

The complications increased with age in both populations for all categories except headache. Since the mean age of the diabetic patients was greater than the controls (mean ± SD = 58 ± 11 vs. 45 ± 15, respectively), the data were subdivided to develop age-matched controls. These results are summarized in figure 2. Although the incidence of nausea, vomiting, severe vomiting, and neurologic complications increased with age, the increase with age was much greater in the diabetics. This same trend was seen when patients were arbitrarily clustered into age group intervals of 10 years, 20

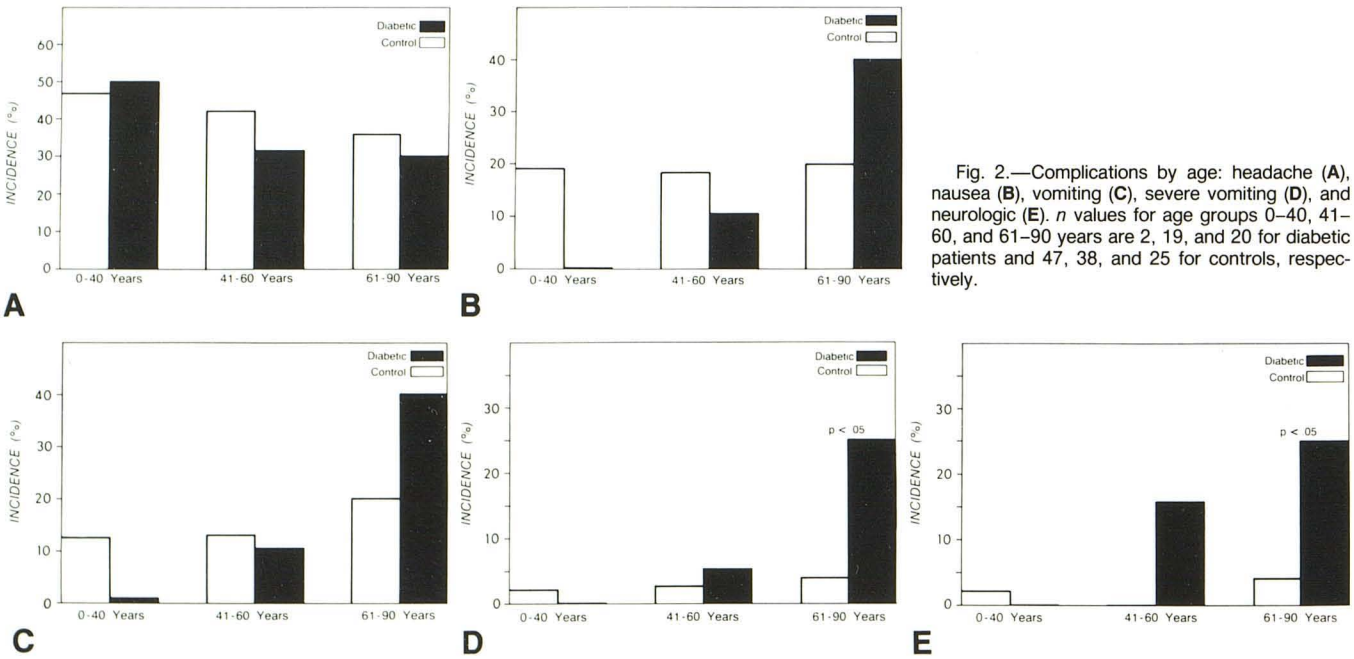

Fig. 2.—Complications by age: headache (**A**), nausea (**B**), vomiting (**C**), severe vomiting (**D**), and neurologic (**E**). n values for age groups 0–40, 41–60, and 61–90 years are 2, 19, and 20 for diabetic patients and 47, 38, and 25 for controls, respectively.

TABLE 1: **Profile of Diabetic Patients Experiencing Neurologic Complications**

Age, Gender	Treatment	Headache	Nausea	Vomiting	Blood Pressure*	Neurologic Disturbance	Duration (hr)†
74, M	PO	...	...	...	NC	Disorientation & severe anxiety	10–24
49, M	PO	Mild	Mild	Mild	NC	Disorientation & felt "strange"	18–24
67, F	I	Moderate	...	...	NC	Somnolent, arousable with difficulty	20–72
56, F	I	Mild	Severe	Severe	NC	Anxiety	Onset unclear; lasted 48
51, F	PO	...	...	...	194/106	Hallucinations primarily auditory, possibly visual	6–24
76, F	PO	...	Moderate	Moderate	200/100	Disorientation (oriented X1)	6–24
71, M	I	Moderate	Severe	Severe	180/100	Encephalopathic, disoriented, incontinent, asterixis	15–120
61, F	I	Severe	Severe	Severe	220/120	Seizures, disoriented, lethargic, incontinent, focal myoclonic seizures, asterixis, ataxia	10–48

Note.—PO = treatment with oral medication; I = treatment with insulin.

* Maximum recorded blood pressure within the 72 hr period after myelography in patients with normal blood pressure or mild hypertension prior to myelography. NC = no change (no indication of major change after myelography).

† Approximate duration of neurologic complication after myelography.

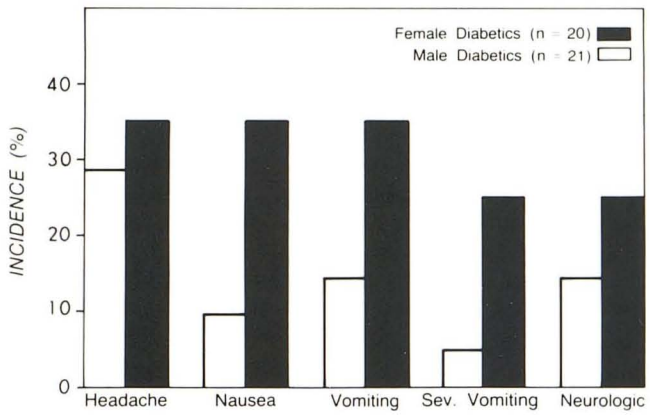

Fig. 3.—Complications in diabetics. Male vs. female.

years, and all patients under 50, compared with all patients over 50.

In 41 diabetic patients, eight well documented neurologic complications were observed (table 1). These included one case each of seizure, severe encephalopathy, hallucinations, prolonged somnolence, and four cases of confusion-anxiety. Two other patients developed symptoms typical for hypoglycemia. These symptoms were promptly relieved with treatment and were considered insulin-induced and not metrizamide related. In the control group, two cases showed the neurologic complication of confusion-disorientation. Four of the diabetic patients showed sustained elevations of blood pressure lasting up to 3 days after myelography.

No statistically significant difference in complications was found between non-insulin-dependent diabetics and the insulin-dependent group. Similarly, we were unable to demonstrate any significant relation of complication rate to other medical risk factors (cardiac disease, hypertension, concurrent medications). Metrizamide doses were similar in both groups ranging from 11 to 17 ml (190 mg I/ml) in the diabetics and 10–17 ml of the same concentration in the controls.

Overall, female diabetics had a higher incidence of all complications than did male diabetics. This was not seen in the control group (fig. 3).

Discussion

This study shows that elderly patients are at a higher risk for protracted vomiting after lumbar metrizamide myelography. In the diabetic patient the risk estimates exceed those of the age-matched controls. Severe vomiting in elderly patients may cause subsequent dehydration, electrolyte imbalance, and secondary neurologic complications. These sequelae may be especially worrisome in diabetics.

A markedly increased risk for neurologic complications is noted for diabetic patients. This risk appears independent of fluctuations in serum glucose levels. For reasons we cannot explain, the risk for neurologic complications in female diabetics was higher than the risk in female controls or male diabetics.

The neurologic complications observed in diabetic patients ranging from neuropsychiatric-type symptoms (confusion-anxiety) to encephalopathy and seizure were similar to symptoms of metrizamide reactions in nondiabetics. Although we cannot exclude fluid and electrolyte imbalance as a contributing factor, vomiting was not always a factor in our patients. Similarly, though clear delineation of the hydration status of patients before myelography was not possible, we have no evidence that our diabetic subgroup had significant electrolyte shifts or dehydration before the procedure.

A high incidence of severe hypertension was also noted in

the diabetic populaton. Blood pressure elevation is not, to our knowledge, mentioned in the literature as a characteristic of metrizamide-induced toxicity in nondiabetics.

Although the mechanism of toxicity of metrizamide is not fully understood, it has been postulated that neurotoxicity is caused by interference with cerebral glucose metabolism [2, 10, 14]. This hypothesis is supported by experiments that demonstrate that metrizamide decreases glucose metabolism in the hippocampus tissue slice model [14] and that in vitro metrizamide is a competitive inhibitor of hexokinase [15]. Diabetics with baseline abnormality of glucose metabolism may be more sensitive than normal patients to a drug that interferes with glucose metabolism.

There also appears to be a close relation between toxic reactions, drug concentration, and time of brain surface contact [3, 7–10]. In one of our diabetics, prolonged high-surface concentrations of metrizamide led to the evaluation and diagnosis of normal-pressure hydrocephalus (NPH). Although we are unable to determine the incidence of NPH in our diabetic study group, diabetics may be at increased risk for NPH. One study reports a fourfold increase in the incidence of abnormal glucose tolerance tests in patients with NPH compared with age-matched controls [16]. One may postulate that basement membrane thickening and associated microvascular changes secondary to diabetes may cause impairment of cerebrospinal fluid synthesis or flow through arachnoid villi.

To our knowledge there are no previous reports of metrizamide complications in the diabetic patient population. However, in a report of two patients who developed metabolic encephalopathy after metrizamide myelography, one patient was diabetic [17]. The Amipaque (metrizamide) index compiled by the Sterling-Winthrop Research Institute, Renssalear, NY, showed no reported cases of seizures in diabetic patients; however, two diabetics developed persistent stupor.

We caution that the diabetic patient population is at increased risk for complications from metrizamide myelography. Toxicity in this group is probably multifactorial, and care should be exercised in studying these patients. Precautionary measures may involve limiting the dose of metrizamide or using the newer and presumably less toxic second-generation nonionic agents when they become available. Initial trials with diabetics will require careful observation.

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