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Diabetes mellitus in normal pressure hydrocephalus

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SUMMARY Seventeen of 33 patients (51.5%) with normal pressure hydrocephalus were discovered to have diabetes mellitus. This was significantly greater than the 12.1% incidence found in age-matched control subjects. The diabetes was not accounted for either by the patients' ages nor by their physical inactivity due to hospitalisation. Diabetes mellitus concurrent with normal pressure hydrocephalus may result from involvement of hypothalamic and brainstem autonomic structures by the expanding ventricles during the evolution of hydrocephalus.

The experiments of Claude Bernard in 1849 first indicated that the central nervous system plays an important role in the regulation of carbohydrate metabolism (Bernard, 1858). A large body of subsequent experimental findings support his observation (Banting *et al.*, 1922; Sacks and MacDonald, 1925; Himwich and Keller, 1930; Macleod, 1934; David *et al.*, 1935; Barris and Ingram, 1936; Anderson *et al.*, 1952; Amand and Dua, 1955). However, there are only rare clinical examples in man in which diseases of the central nervous system are regularly associated with glucose abnormalities (Matthews, 1958; Steinke and Taylor, 1964; Schalch *et al.*, 1970). In this study, a remarkably high incidence of diabetes mellitus was found in patients with the syndrome of normal pressure hydrocephalus. This is the first evidence that normal pressure hydrocephalus may be one of the unusual instances in which the brain's influence on glucose metabolism becomes manifest in a disease state.

Patients and methods

CLINICAL-RADIOGRAPHIC CRITERIA FOR DIAGNOSIS OF NORMAL PRESSURE HYDROCEPHALUS

The diagnosis of normal pressure hydrocephalus was made in 33 patients (50–84 years). In each case the diagnosis was made on the basis of the clinical picture and the radiographic findings. These patients had combinations of organic dementia (deficits of memory, orientation, calculations, reversals of serial orders, positive face-hand tests), motor dysfunction (gait disturbance, extrapyramidal), and incontinence. The presence of all three signs was not required for the diagnosis. The combinations of clinical signs are summarised in Table 1.

Table 1 *Combinations of clinical signs in the 33 normal pressure hydrocephalus patients not previously suspected of having diabetes mellitus*

Combinations of signs	*Patients*
Dementia, motor dysfunction, incontinence	18
Dementia, motor dysfunction	3
Dementia, incontinence	7
Motor dysfunction, incontinence	4
Motor dysfunction	1
Total	33

Every patient underwent pneumoencephalography (30–65 ml), and radioisotopic cisternography. The characteristic appearance of the pneumoencephalogram was essential for the diagnosis. There was always enlargement of the ventricles, with no air over the convexities of the cerebral hemispheres. There was never pneumoencephalographic evidence of cortical atrophy or obstruction of the ventriculo-aqueductal system. Cisternography was performed by injection of radiopharmaceutical (iodinated ^{131}I serum albumin in six, and ^{169}ytterbium in 27

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patients) into the lumbar subarachnoid space. Serial images were obtained at four, 24, and 48 hours in the lateral and anterior positions. The cisternograms were abnormal in every patient. Abnormal patterns were classified as (1) 'characteristic' of normal pressure hydrocephalus—ventricular stasis after 24 and 48 hours with no activity over the convexity—24 patients, or (2) 'mixed'—activity in the midline cisterns, or slow flow of activity in the Sylvian regions combined with some degree of ventricular retention—nine patients. The diagnosis of normal pressure hydrocephalus was not made if there was accumulation of radioactivity over the convexities or parasagittal regions after 24 and 48 hours. The clinical, radiographic, and surgical response profiles of 25 of these patients have been reported in detail elsewhere (Jacobs *et al.*, 1976; Jacobs and Kinkel, 1976). Another five patients have subsequently undergone shunt surgery; three remain unoperated. Six other patients who fulfilled the clinical and radiographic criteria for the diagnosis of normal pressure hydrocephalus were known diabetics who were already taking medications. They were excluded from this study which was limited to normal pressure hydrocephalus patients who were not previously suspected of having diabetes mellitus.

CRITERIA FOR DIAGNOSIS OF DIABETES MELLITUS

Oral glucose tolerance tests (GTT) were conducted on every patient. The test was performed on 20 patients before cisternography, pneumoencephalography, or ventricular shunting procedures. Three patients underwent GTT after they had been discharged from hospital, and long after these stressful procedures had been performed (24, 28, 36 months), when the risk of a pseudodiabetic response was felt to be minimal. Patients were well fed on high caloric diets (200 g of carbohydrate) for three days before the test. They drank Glucola solution, (75 g glucose, Ames) after an overnight fast. Collection of blood samples was by the Janney-Isaacson method (Helper, 1966), with blood drawn from the antecubital vein, and plasma glucose levels were determined by colorimetry (Dow). The plasma glucose values (mg/dl) were also converted into SI Units (mmol/l) (National Bureau of Standards, 1972). Fasting, one, two, and three-hour samples were drawn. The GTT were interpreted by the Wilkerson point system, with the critical values changed in accordance with the use of plasma rather than whole blood (Klimt *et al.*, 1969). Scoring of glucose levels by this system is: Fasting $>$ 130 mg/dl = 1 point, one hour $>$ 190 mg/dl = $\frac{1}{2}$ point, two hour $>$ 140 mg/dl = $\frac{1}{2}$ point, three hour $>$ 130 mg/dl = 1 point. The SI scoring is: Fasting $>$ 7.2 mmol/l = 1 point, one hour $>$ 10.5 mmol/l = $\frac{1}{2}$ point, two hour $>$ 7.7 mmol/l = $\frac{1}{2}$ point, three hour $>$ 7.2 mmol/l = 1 point. The diagnosis of diabetes mellitus was made only if the patient's score was 2 or greater.

In addition, the two hour glucose levels were compared with a standardised nomogram which adjusts two hour whole blood glucose elevations in a large non-hospitalised population (Andres, 1971). The plasma levels were reduced by 14% for comparison with the whole blood glucose values (Zalme and Knowles, 1965).

Glucose tolerance tests (using the same criteria for the diagnosis of diabetes) were also conducted on 33 control subjects with non-neurological disorders. Control subjects were otherwise randomly selected. They were hospitalised for degenerative disc disease (eight), bone fracture (seven), and elective hernia surgery (six). Twelve had no medical illness at the time of the GTT and were awaiting placement in a nursing facility. The sex distribution of controls and normal pressure hydrocephalus patients was similar.

Results

Table 2 shows the two hour plasma glucose levels of normal pressure hydrocephalus and control patients. Seventeen of the 33 normal pressure hydrocephalus patients (51.5%) had elevated two hour levels and fulfilled the other criteria for the diagnosis of diabetes mellitus. Another nine had two hour elevations but did not fulfil the other criteria for the diagnosis. Four (12.1%) of the control patients had two hour elevations and other criteria indicating diabetes; another six had elevations of the two hour glucose, but did not fulfil the other criteria for the diagnosis. The incidence of diabetes was significantly different in the two groups ($P < 0.01$). When abnormal GTT occurred, the degree of plasma glucose elevation was greatest in normal pressure hydrocephalus patients. The average two hour level in patients considered diabetic was 233 mg/dl (range 168–400 mg/dl) in normal pressure hydrocephalus patients, and 197 mg/dl (range 173–214 mg/dl) in controls (not significant). The average SI two hour value was 12.8 mmol/l (range 9.2–22.2 mmol/l) in normal pressure hydrocephalus patients, and 10.8 mmol/l (range 9.5–11.8 mmol/l) in controls. Comparison of the corrected—that is, 14% reduction—plasma two hour glucose levels to the age-adjusted nomogram based on whole blood glucose levels showed an average percentile ranking of 17.2% (range 0–49%) for the normal pressure hydrocephalus patients, and 30.5% (range 17–50%) for the controls. Thus, 82.8% of normal subjects of similar ages would be expected to have lower two hour levels than the normal pressure hydrocephalus patients while 69.5% would be expected to have lower levels than the controls.

Table 2 *Two hour plasma glucose levels in normal pressure hydrocephalus patients and controls. Diabetes occurred in seventeen (51.5%) of normal pressure hydrocephalus patients, but only four (12.1%) of controls* ($P < 0.01$). *The scoring system is described in the text*

Normal pressure hydrocephalus						*Controls*					
			Two hour glucose						*Two hour glucose*		
Case	*Sex*	*Age (yr)*	*(mg/dl)*	*(mmol/l)**	*Considered diabetic*	*Case*	*Sex*	*Age (yr)*	*(mg/dl)*	*(mmol/l)**	*Considered diabetic*
1	M	50	120	6.7	No	1	M	50	76	4.2	No
2	F	57	203	11.3	Yes	2	M	55	118	6.5	No
3	F	57	190	10.5	Yes	3	F	56	77	4.3	No
4	M	60	165	9.2	No	4	F	60	103	5.7	No
5	M	61	256	14.2	Yes	5	M	60	69	3.8	No
6	M	61	204	11.3	No	6	F	63	120	6.7	No
7	F	63	168	9.3	Yes	7	M	64	146	8.1	No
8	M	66	320	17.8	Yes	8	M	65	124	6.9	No
9	F	67	180	10.0	Yes	9	F	66	71	3.9	No
10	M	67	116	6.4	No	10	M	67	103	5.7	No
11	F	67	240	13.3	Yes	11	F	67	97	5.4	No
12	M	68	150	8.3	No	12	M	68	145	8.0	No
13	M	68	195	10.8	Yes	13	F	68	200	11.1	Yes
14	M	69	164	9.1	No	14	M	69	116	6.4	No
15	F	69	167	9.3	No	15	M	71	100	5.6	No
16	F	70	124	6.9	No	16	F	72	80	4.4	No
17	M	72	182	10.1	Yes	17	M	72	214	11.8	Yes
18	F	72	162	9.0	No	18	M	73	120	6.7	No
19	M	72	165	9.2	No	19	F	73	110	6.1	No
20	F	73	247	13.7	Yes	20	M	74	68	3.8	No
21	M	74	165	9.2	No	21	M	74	80	4.4	No
22	F	74	120	6.7	No	22	M	75	126	7.0	No
23	M	74	135	7.5	No	23	F	75	178	9.9	No
24	F	74	135	7.5	No	24	M	77	145	8.0	No
25	M	75	400	22.2	Yes	25	M	77	106	5.9	No
26	M	77	170	9.4	No	26	F	77	86	7.8	No
27	F	77	236	13.1	Yes	27	M	77	178	9.9	No
28	F	77	251	13.9	Yes	28	F	78	201	11.2	Yes
29	M	79	175	9.7	Yes	29	M	78	118	6.5	No
30	F	79	134	7.4	No	30	M	79	120	6.7	No
31	M	82	197	10.9	Yes	31	M	81	162	9.0	No
32	F	84	254	14.1	Yes	32	F	82	111	6.2	No
33	F	84	272	15.1	Yes	33	F	84	173	9.6	Yes

*SI Units.

Comment

The compelling evidence for a definite relationship between diabetes mellitus and normal pressure hydrocephalus was the frequency with which diabetic GTT occurred in normal pressure hydrocephalus patients (51.5%) compared with controls (12.1%). The incidence of diabetes in controls was slightly above the 6–7% prevalence reported for the age groups studied (Joslin, 1971), while that of the normal pressure hydrocephalus patients was approximately eight times greater than the expected prevalence.

Normal pressure hydrocephalus occurred in an older population. Abnormal GTT are found with increasing frequencies in older subjects who have no other signs of diabetes (Andres, 1971; Unger, 1957; Malins *et al.*, 1963; Andres, 1971). However, the diabetes mellitus in these patients was not accounted for by their advanced ages, because comparison of their two hour glucose levels with the age-adjusted nomogram (Andres, 1971) revealed that their elevations were in excess of those attributable to increasing age. Hospitalisation, with subsequent physical inactivity, may result in a 'chemical diabetes' which disappears as soon as normal activity is resumed (Andres, 1971). However, hospitalisation-inactivity did not account for the 40% discrepancy in incidence of diabetes between the normal pressure hydrocephalus and control patients, because the control group came from a hospitalised population, many of whom had been in hospital for months. Thus, the relationship between normal pressure hydrocephalus and the diabetic state is not accounted for either by age or hospitalisation.

The earliest descriptions of normal pressure hydrocephalus hypothesised that the intraventricular pressure was elevated at an early stage in the development of the syndrome (Hakim and Adams, 1965; Adams *et al.*, 1965). Subsequent studies of the temporal sequence of events leading to normal pressure hydrocephalus in dogs support this concept (James *et al.*, 1973). Following subarachnoid injection of silastic, the intraventricular pressure initially increased as the ventricles enlarged. After 20–40

days, the pressure gradually returned to normal but the ventricles remained enlarged. In most cases in humans the enlargement is generalised and includes lateral, third, and fourth ventricles as well as the aqueduct of Sylvius. As the expansion progresses, there must be compression of adjacent diencephalic and brainstem structures. Electric stimulation and ablation studies of hypothalamus, midbrain, and floor region of the fourth ventricle have produced hyperglycaemia and glycosuria in animals (Bernard, 1858; Banting *et al.*, 1922; Sacks and MacDonald, 1925; Himwich and Keller, 1930; Macleod, 1934; David *et al.*, 1935; Barris and Ingram, 1936; Anderson *et al.*, 1952; Amand and Dua, 1955). In man, diabetes mellitus has occurred in conjunction with cysts or neoplasms of the midbrain, dienphalon, and roof of the third ventricle (Byrom and Russell, 1932; Vonderahe, 1937; Beck *et al.*, 1966). In a remarkable case of intermittent aqueductal obstruction, there was severe diabetes mellitus which worsened with each acute exacerbation of internal hydrocephalus and resolved each time the pressure was relieved (Niemer and Vonderahe, 1940).

The same physiological mechanism may be at the basis of the diabetes mellitus produced experimentally and that occurring spontaneously in hydrocephalus, namely destructive or irritative involvement of hypothalamic and brainstem autonomic structures which carry glycogenolytic impulses to the liver, or supply the pituitary, adrenals, or pancreas (Best, 1961; Haymaker and Anderson, 1973). However, in most previous cases of hydrocephalus with diabetes mellitus, the hydrocephalus was acute, and the intraventricular pressure elevated. The same explanation may not apply in cases of normal pressure hydrocephalus where the hydrocephalus is more chronic and the intraventricular pressure has returned to normal.

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