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Pseudotumor Cerebri: Clinical and Neuroradiological Findings

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Summary. Pseudotumor cerebri (PTC) is a diagnosis *per exclusionem* applied to a condition of increased intracranial pressure in the absence of an intracranial infection, a space-occupying lesion, or hydrocephalus. Diagnostic criteria should include the evaluation of possibly disturbed cerebral venous outflow, which may result in similar clinical findings. Disturbed venous drainage should be separated from the syndrome of PTC because it represents a condition of well-defined origin and therapeutic regimen. Course and prognosis of PTC are not related to the increased intracranial pressure, the degree of papilledema, or to the duration of the disease. Functional cerebral disorders and EEG abnormalities are rare, indicating that brain tissue is not primarily affected. Correspondingly, computerized tomography (CT) scans with respect to the cerebrum are normal in about 90% of the cases; but enlarged optic nerve sheaths (46.7%) and empty sella (45.7%) are frequent findings on CT-scans. They most likely represent a direct consequence of long-term increased pressure within CSF spaces. This observation favors the assumption of disturbed CSF pressure regulation either by increased production of CSF or its decreased rate of absorption. Brain edema (slit ventricles) as assessed by CT is a rare finding (11.4% of our cases). It may be a hint towards a different pathogenetic entity.

Key words: Pseudotumor cerebri – Computerized tomography – Empty sella – Disturbed CSF circulation – CSF pressure

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Introduction

The syndrome of pseudotumor cerebri (PTC) is characterized by increased intracranial pressure usually without focal signs of neurological dysfunction except for visual signs due to papilledema. Diagnostic criteria besides increased CSF pressure are absence of an intracranial infection and exclusion of an intracranial space-occupying lesion or hydrocephalus [1, 30]. Headache, nausea, vomiting, and obscurations are the dominant symyptoms. The most important finding is chronic bilateral papilledema [1, 2, 30]. The pathophysiological mechanism of PTC is obscure and probably not uniform. Hypotheses are (1) a decreased rate of CSF absorption, (2) an increased rate of CSF formation, (3) an increase in brain volume or interstitial fluid volume simulating brain edema, and (4) a sustained increase in intracranial venous pressure [15, 17]. Conditions such as menstrual irregularities, pregnancy, endocrine disturbances, oral contraceptives, corticosteroid therapy and its withdrawal, nitrofurantoin, nalidixic acid, and tetracycline therapy, anemia, hyper- and hypovitaminosis A, spinal cord tumors, and Guillain-Barré syndrome have been described as associated with PTC [1, 17]. Disturbance of cerebral venous outflow by sinus thrombosis was shown to be one mechanism which may lead to the clinical syndrome of PTC [3, 8, 17, 27, 32] (pathophysiological mechanism 4). In our own series of extensive superior sagittal sinus thrombosis 6 out of 14 patients presented with signs of increased intracranial pressure exclusively [32]. According to Ahskog and O'Neill [1] this disorder should be separated because it represents a different condition. Facultative CT

signs in PTC such as narrow CSF spaces, empty sella, and enlargement of optic nerve sheaths have been described repeatedly [5, 28, 29, 35]. A small-sized ventricular system as a consequence of increased brain volume, i.e., brain edema, has been reported in some of the PTC cases examined by CT [28, 35], suggesting the mechanism of hypothesis 3. In cases without sinus thrombosis and brain edema, representing the major proportion of PTC patients, primary elevation of CSF pressure (hypothesis 1 and 2) has to be assumed. In order to further elucidate these points we reviewed the clinical and neuroradiological findings of 35 patients with PTC retrospectively.

Patients and methods

PTC was diagnosed in 35 patients hospitalized between 1982 and 1986. All patients underwent careful neurological and ophthalmological testing and at lest two follow-up examinations. The diagnosis was based on (1) papilledema, (2) increased intracranial pressure, (3) normal CSF composition and (4) exclusion of a space-occupying lesion or hydrocephalus by computerized tomography (CT). Six cases initially diagnosed as PTC had extensive sinus thrombosis as shown by angiography and were excluded from this series [32].

From 1982 to 1984 a Siretom head scanner (256 × 256 matrix) was used (slice thickness 0.5 to 1 cm). From 1985 a high resolution Somatom DRH Scanner (512 × 512 matrix) was available (slice thickness for scans of the orbit and sella 0.2 to 0.4 cm). CT evaluation by visual inspection was done by two independent experienced examiners including an assessment of optic nerves, sella, and brain volume (small-sized ventricular system and external CSF spaces). Evaluation of the CT scans was restricted to statement of normal or pathological findings. The diagnosis of empty sella was based on the combination of enlarged sella, normally located pituitary stalk, and CSF density within the sella. In cases of nonaccordance of the two examiners, a third neuroradiologist was consulted. Due to the retrospective character of the study special scans of the orbit were not available in all cases between 1982 and 1984. In order to exclude superior sagittal sinus thrombosis additional contrast CT studies were done in 25 patients; in 12 of the 35 cases with PTC an angiography was performed by conventional or digital subtraction technique. To differentiate cystic pituitary tumor from empty sella CT cisternography was carried out in 1 case by giving 8 ml of nonionic contrast medium (iodine concentration 200 mg/ml) by lumbar puncture.

In 6 patients magnetic resonance imaging (MRI) was performed using a 1.5 Tesla Magnetom (Siemens, Erlangen, FRG) and a special head coil with a diameter of 30 cm. Using the spin-echo technique, T1-weighted images (TR = 400 ms, TE = 30 ms) and T2-weighted images (TR = 1600 ms, TE = 60 ms) in the frontal and sagittal planes were obtained. Additionally T2 values were calculated by linear regression of 16 echos. Slice thickness was 0.6 to 0.8 cm.

Lumbar puncture was invariably performed without premedication and without local anesthesia using a 0.9 mm needle at the L3/L4 interspace. From 1982 to 1984 lumbar puncture was done on patients sitting up, since 1984 on patients lying on one side. The manometer was attached with an estimated loss of less than 1 ml of CSF. Pressure was measured with a closed manometer, the pressure recorded was stable for a full minute. Sitting patients were positioned with the neck carefully extended and the legs passively posed in a comfortable and relaxed position, lying patients were posed in a relaxed lateral decubitus position. Ten patients with no evidence for increased intracranial pressure who underwent a diagnostic lumbar puncture for encephalomyelitis disseminata, matched in sex and age, were used as controls.

Results

The mean age of the 35 patients was 38.5 years, 30 were female, 5 male; 57.1% were obese with a Broca index of more than 1.2

$$\left(\text{Broca index} = \frac{\text{weight (kg)}}{\text{height (cm)} - 100}\right).$$

Menstrual irregularities (5.7%), pregnancy (2.9%), oral contraceptives (8.6%), endocrine disturbances (2.9%), and steroid medication (2.9%) were rarely observed.

Neurological Findings

According to the definition of PTC all patients had increased CSF pressure, as revealed by lumbar puncture (Table 1, Fig. 1). The upper limit of normality was defined as 250 mm H_2O in patients sitting up or lying down [14]. Intracranial pressure was at the limit or slightly increased in 6 cases and markedly increased in 29 cases (Fig. 1). Mean CSF pressure was significantly increased ($P < 0.01$) in patients with PTC tested sitting up (484 mm H_2O) or lying (424 mm H_2O) respectively as compared to normal controls (171 mm H_2O sitting, 116 mm H_2O lying) [36].

Table 1. Clinical symptoms and signs in 35 patients with pseudotumor cerebri

	n	(%)
Increased intracranial pressure (lumbar puncture)	35	100
Clinical signs for increased intracranial pressure (headache, nausea, vomiting)	26	74.3
Papilledema	35	100
Obscurations	16	45.7
Visual loss (decreased acuity)	15	42.9
Visual field deficits	27	77.1
6th nerve palsy	3	8.6
Transient somato sensory signs	7	20.0
EEG changes	4 (out of 29)	13.8

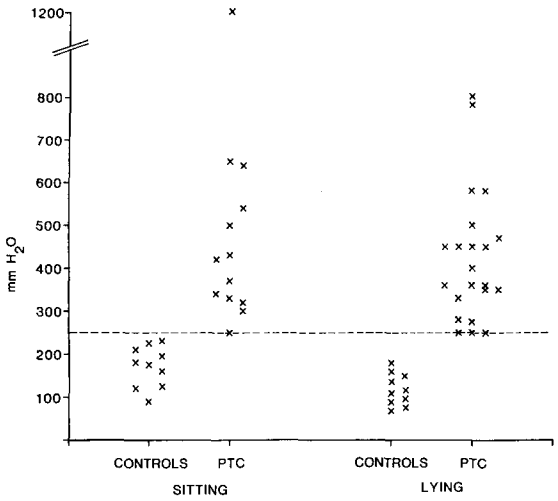

Fig. 1. CSF pressure values (mm H_2O) as measured by lumbar puncture on sitting ($n = 13$) or lying ($n = 22$) pseudotumor cerebri (PTC) patients and control subjects ($n = 10$). (---) = upper limit of normality

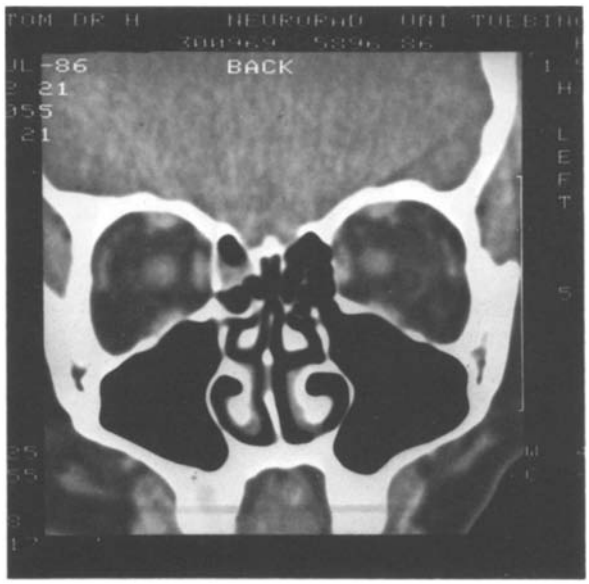

Fig. 2. Coronal computerized tomography (CT) of the orbit shows enlargement of both optic nerves as a frequent finding in cases of PTC on high resolution scans. Slice thickness 2 mm

All patients had chronic papilledema (Table 1). In 4 cases, after a history of papilledema, bilateral subtotal optic atrophy had developed in the course of the disease (mean duration 7 years). Papilledema ranged from mild to severe up to a prominence of 6 dpt. Correlation between the actually measured intracranial pressure and the degree of papilledema (dpt.) was poor ($r = 0.43$). The incidence of other symptoms and signs is shown in Table 1. Headache often combined with nausea and vomiting was most common. Other signs were primarily restricted to vision with visual field deficits (peripheral visual field deficits, usually nasal at the beginning) and reduced visual acuity. Obscurations as forerunners of permanent visual deficits and visual loss occurred in about 50% of patients [2]. Sixth nerve palsies and transient somatosensory signs were relatively rare. EEG abnormalities occurred in 13.8% of cases. Two times slowing of background activity was seen, one case showed focal discharge and another paroxysmal discharge of sharp slow wave complexes. Eight additional cases had a slow frequency between 7 and 8 Hz. The CSF (cell count, CSF protein) was normal,

Table 2. CT findings in 35 patients with pseudotumor cerebri

	n	(%)
Enlarged optic nerves	14 (out of 30)	46.7
Empty sella	16	45.7
Brain edema (small-sized ventricular system)	4	11.4

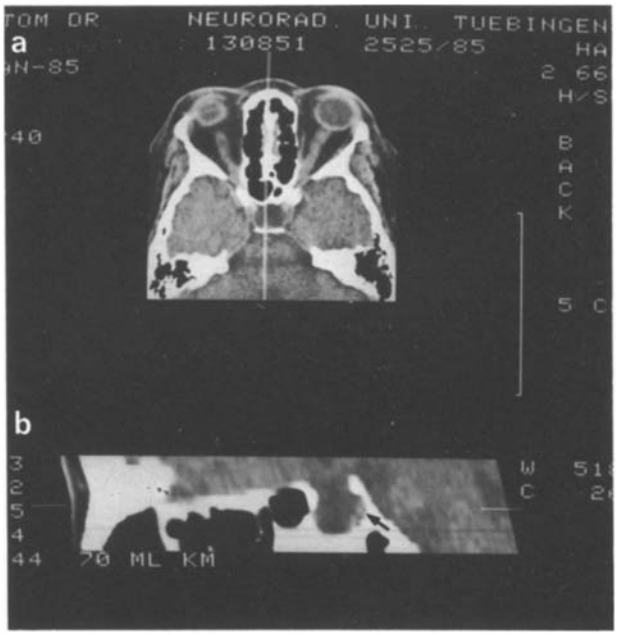

Fig. 3. Contrast-enhanced axial CT scans **(a)** show enlargement of the optic nerves and of the sella. CSF densities occupy most of the sellar volume. On the sagittal reformatted image **(b)** the remaining pituitary gland can be seen flattened against the posterior aspect of the dorsum *(arrow)*

except for one case, in which several controls presented abnormal mitotic cells but normal CSF protein content and cell count. There has been no evidence of a tumor in the further course of up to 12 months.

CT Findings

The CT findings of the 35 patients with PTC are shown in Table 2. Enlarged optic nerves were found in 46.7% of the cases that had orbital scans (Figs. 2, 3a and 4a). With the high resolution scanner used since 1985 enlarged optic nerves were an even more frequent finding.

Empty sella was diagnosed in 45.7% of the cases (Figs. 3a and b, 4a and b). Figures 3b and 4b shows compression of the pituitary gland by herniation of the subarachnoid space into the sella turcica. Intracranial pressure was significantly ($P < 0.01$) increased in patients with empty sella (mean 519 mm H_2O) as compared to the PTC cases without empty sella (mean 385 mm H_2O).

A small-sized ventricular system, narrow external CSF spaces, and hypodensity of the white matter, suggesting brain edema, was only found in 4 out of 35 cases. Three of these cases had severe brain edema with slit-like ventricles and compression of the basal cisterns and subarachnoid spaces over the cerebral convexities. The other patient showed mild to moderate brain edema. There was no correlation between

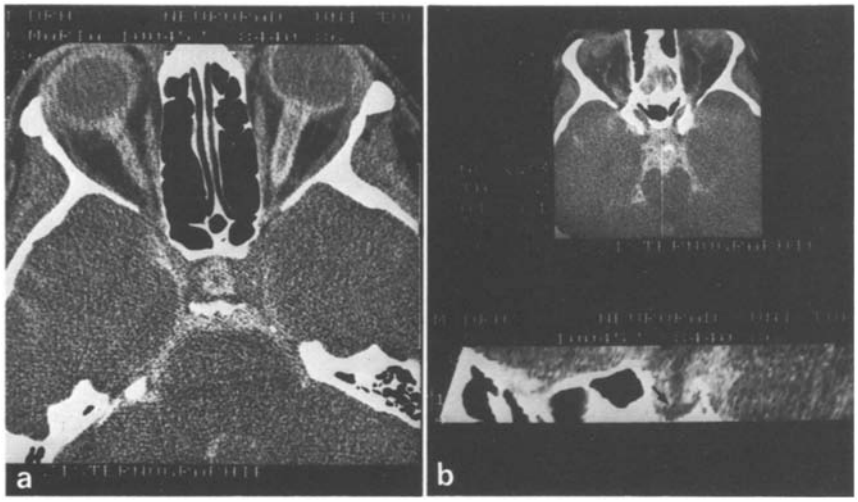

Fig. 4. Computerized axial cisternography **(a)** with sagittal reformatted image **(b)**. There is free communication between supra- and intrasellar subarachnoid spaces. The pituitary stalk is stretched, the pituitary gland is flattened against the sellar floor *(arrow)*. There is marked distension of the subarachnoid spaces around the optic nerve on the right. On the left side optic nerve sheaths fenestration was performed 2 days before this examination. Slice thickness 1 mm

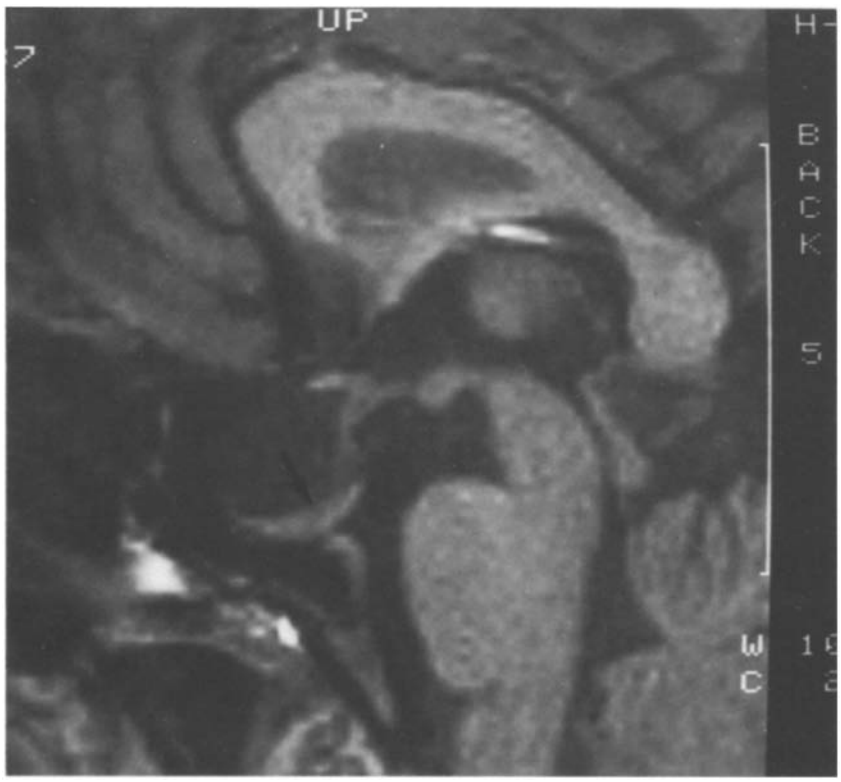

Fig. 5. Sagittal magnetic resonance image of enlarged sella. Most of the pituitary fossa is occupied by CSF space not due to enlargement of the infundibular recessus. The pituitary gland is flattened against the sellar floor *(arrow)*. Slice thickness 2 mm (400 ms TR, 24 ms TE)

the finding of brain edema and the amount of intracranial pressure. Angiography was not performed in any of these 4 patients, examined within the first 2 years of this retrospective study, to exclude sinus thrombosis.

MRI Findings

MRI findings with respect to the brain tissue were normal in all 6 cases. No signs of brain edema, periventricular alterations, or abnormal T2 relaxation times of the white matter could be found. Sellar pathology was demonstrated by MRI (Fig. 5) as well as using CT cisternography. Differentiation between pituitary adenoma and herniation of CSF spaces into the sella was possible by this technique.

Discussion

The patients in the present series were representative of the clinical syndrome of PTC as described by previous authors [2, 6, 11, 13, 21, 23, 28, 29, 35]. Previous series, however, may not be fully comparable with our patients since the diagnosis depends on the criteria mentioned above, which were not always applied in the same way. We looked carefully for signs of sinus thrombosis during the last 3 years of the study and excluded cases with extensive thrombosis of venous sinuses [32].

The association of PTC with menstrual irregularities, pregnancy, endocrine disturbances, oral contraceptives, steroid medication, and other disturbances has been stressed by many authors [1]. In our patients a causative relation could not be shown for any of these occasionally observed conditions. We therefore suppose, that there is only a coincidental association except for the possibility that endocrine disturbances may result from pituitary compression following increased intracranial pressure and herniation of the subarachnoid space into the sella turcica, as indicated in some of our cases (Fig. 3b, 4b, 5). On the other hand the significance of the female preponderance and the high rate of obesity in PTC patients indicates a causative relationship of unknown etiology.

It is almost impossible to firmly date the onset of PTC, complaints are not a useful measure of the duration of the disease [13, 29]. We did not find a correlation between intracranial CSF pressure and the degree of papilledema. According to previous studies visual failure is not related to the amount of disc swelling [23, 29]. The prognosis therefore does not seem to correlate with the measured increased intracranial pressure, the degree of papilledema, or the duration of the disease. This observation enforces the clinical practice stating that operative procedures in order to relieve increased intracranial pressure are only recommended in cases with progressive loss of visual function despite recurrent lumbar punctures [33]. Psychopathological symptoms such as affective disorders, organic syndrome [26], and alteration of consciousness [23] were not obvious in our patients and are rarely reported in the literature. In accordance with previous EEG studies [11, 23, 29, 31] only few patients had abnormal EEGs (13.8%). This perhaps infers that intracranial compartments other than brain tissue are primarily affected in PTC. The occurrence of psychopathological symptoms and EEG abnormalities therefore should stress investigation for other reasons of increased intracranial pressure.

Although enlarged sella and other signs of increased intracranial pressure were described in the early 1970s on skull roentgenogramms and by pneumencephalography [4, 19, 34], initial CT studies in PTC did not yield any pathological findings [13, 16, 22]. In contrast the recent investigation by Weisberg [35] described abnormal CT findings in 36% of PTC patients, concerning optic nerves, sella, and CSF spaces.

In our series optic nerves appeared to be enlarged in 46.7% of cases. Enlargement of the optic nerve sheath is due to distension of the subarachnoid spaces around the optic nerve, as was demonstrated by CT cisternography (Fig. 4a). Using echography enlargement of the spaces between the optic nerve and its sheath has been shown in all cases with PTC [2]. Using a high resolution CT scanner and performing adequate orbital scans we would expect a corresponding rate of pathological optic nerve findings.

In accordance with a previous paper [5] we found an empty sella in about half of our patients (45.7%) (Figs. 3, 4, 5). In cases of considerably enlarged sella water soluble CT cisternography (Fig. 4) or MRI (Fig. 5) is needed to differentiate cystic pituitary tumor from primary empty sella [7]. The pathogenetic mechanism seems to be an intrasellar herniation of CSF spaces in cases of absent or open diaphragma sellae, favored by raised intracranial pressure [7, 9, 19, 25]. Our finding of a correlation between the amount of intracranial pressure and the incidence of empty sella together with evidence for pituitary compression by herniation of the subarachnoid space into the sella turcica in some CT scans (Figs. 3b, 4b) and MRI (Fig. 5) supports this pathogenetic theory. A possible herniation of the optic chiasm into the sellar fossa was suggested by Foley and Posner [19] to be an additional mechanism to papilledema leading to visual abnormalities. From pathoanatomical studies an increased incidence of incompetent sellar diaphragma

in women has been shown [12], and may explain the high preponderance of women with PTC.

Unlike most of the previous CT studies in PTC [13, 16, 22, 29] a high rate of small ventricles was reported by Weisberg [35] in 21% of the cases and in the series of Reid et al. [28] in 10 out of 15 patients. As patients with PTC are relatively young (mean age 38.5 years in our series) subarachnoid spaces and ventricles are age-related small, so that the incidence and significance of narrow CSF spaces may be overestimated. We found narrow CSF spaces, suggesting brain swelling, in only 4 out of 35 patients (11.4%). In the majority of our cases (88.5%) neither narrowing of CSF spaces nor hypodensity of the white matter [28, 35] was observed, as should be expected in brain edema. Additionally our MRI investigations demonstrated normal findings with respect to brain tissue. Although determination of T2 relaxation times may not be refined enough to demonstrate small fluctuations in the free water compartment of the brain, our findings and those of previous studies [13, 16, 22, 29] argue against brain swelling as the main pathogenetic factor in most cases of PTC. As described previously [32] brain edema was found in 2 out of 6 cases excluded from this series for having sinus thrombosis. Therefore, if brain edema is found, exclusion of disturbed venous drainage is mandatory and other pathogenetic conditions should be considered [15, 17, 37].

The undoubted efficacy of lumbar puncture in PTC suggests the CSF compartment as primarily expanded. The mostly unchanged brain function in terms of rare psychopathological disturbances and EEG abnormalities as compared to increased intracranial pressure of other causes [31] fits this assumption. Out data and previous investigations on cerebral hemodynamics and CSF circulation [9, 10, 20] suggest a disturbed production or absorption of CSF with increased CSF pressure to be causal in the pathogenesis of PTC.

Our data suggest the following diagnostic procedure in clinically and neuroradiologically suspected cases: CT examination should include contrast-enhanced CT, and if there is a suspicion of sinus thrombosis angiography should be performed. To differentiate cystic tumor from empty sella CT cisternography has to be recommended in some cases. MRI may be helpful in the diagnostic evaluation of sellar pathology and of the small group of patients presenting with brain edema of unknown etiology.

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