Although the association of endocrine dysfunction and hydrocephalus was first observed in 1913, the destruction of the sella turcica, a radiographic finding that suggests pituitary pathology, was not reported until 1930. The first operation performed in a patient reported to have amenorrhea and hydrocephalus was a third ventriculostomy, which was performed via open craniotomy in 1951; following the procedure the patient experienced resumption of normal menses. Twenty patients who presented with amenorrhea associated with hydrocephalus have previously been described in the literature. All those reported to have undergone surgical treatment had resolution of their amenorrhea (Table 1). All but two patients had primary amenorrhea, the failure of menarche by the age of 16 years. Two other cases of secondary amenorrhea (the absence of menses in a patient who previously menstruated) have previously been described in the literature. All those reported to have undergone surgical treatment had resolution of their amenorrhea (Table 1). Although the association of endocrine dysfunction and hydrocephalus was first observed in 1913, the destruction of the sella turcica, a radiographic finding that suggests pituitary pathology, was not reported until 1930. The first operation performed in a patient reported to have amenorrhea and hydrocephalus was a third ventriculostomy, which was performed via open craniotomy in 1951; following the procedure the patient experienced resumption of normal menses. Twenty patients who presented with amenorrhea associated with hydrocephalus have previously been described in the literature. All those reported to have undergone surgical treatment had resolution of their amenorrhea (Table 1). All but two patients had primary amenorrhea, the failure of menarche by the age of 16 years. Two other cases of secondary amenorrhea (the absence of menses in a patient who previously menstruated) were described by Fossati, et al. in 1955 and by Jawadi, et al., in 1979. Jawadi, et al., found this association in a patient who also had a hypothalamic astrocytoma, which contributed to the development of amenorrhea. The case presented here is the first report of secondary amenorrhea and hydrocephalus in a tumor-free patient who experienced resolution of her symptoms following surgery.

Case Report

This 32-year-old woman presented in June 1993 with secondary amenorrhea that had lasted 1 year.

History. The patient had undergone menarche at the age of 13 years, following which she had been eumenorrheic. She had cyclic withdrawal bleeding while receiving a 10-year course of oral contraceptives started at age 21 years. She discontinued the use of oral contraceptives to attempt pregnancy but remained amenorrheic. Further questioning revealed a 3-year history of fatigue and decreased libido but no galactorrhea. She also underwent a successful 20-lb weight loss achieved with dieting and exercise. Additionally, she had been given levothyroxine therapy (0.1 mg daily) following the discovery of a borderline low thyroid-stimulating hormone (TSH) 1 year prior to presentation.

Examination. Physical examination at presentation showed that the patient weighed 110 lbs and was 5 ft 1 in tall. She had a nonpalpable thyroid gland, Tanner stage four breast development, and a normal female adult body hair pattern. Her pelvic examination was normal, with the cervix noted to be well estrogenized and the uterus retroverted and of normal size. Pelvic ultrasonography revealed small ovaries with multifollicular cysts consistent with chronic anovulation, and the uterine lining was 5 mm in thickness, a normal width.

Endocrinological evaluation revealed a low TSH (0.1 mU/L) and T3 (1.06 nmol/L) but a normal thyroxine (T4) (7.6 μg/dl). Her prolactin (4.5 ng/ml) and morning cortisol (16 μg/dl) levels were both normal. Follicle-stimulating hormone (FSH) (3.4 IU/L), luteinizing hormone (LH) (0.7 IU/L), and estradiol (< 10 pg/ml) were all below normal levels. Pregnancy was excluded by a negative urine human chorionic gonadotropin (hCG) sample. Because the low TSH level with a normal T4 level suggested sup-
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<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs)</th>
<th>Amenorrhea</th>
<th>Cause of Hydrocephalus</th>
<th>Treatment</th>
<th>Outcome</th>
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<tr>
<td>Davidoff &amp; Epstein, 1950</td>
<td>18</td>
<td>primary</td>
<td>CAS</td>
<td>open ventriculotomy</td>
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<td>—</td>
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<td>Kim, et al., 1969</td>
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<td>Chiari I malformation</td>
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<td>shunt</td>
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<td>—</td>
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<td>CAS</td>
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<tr>
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<td>4th V obstruction</td>
<td>VA shunt</td>
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<td>CAS</td>
<td>VA shunt</td>
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<td>—</td>
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<td>secondary</td>
<td>ventriculocisternostomy</td>
<td>resolved, 8 mos</td>
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</tbody>
</table>

*CAS = cerebral aqueductal stenosis; V = ventricle; VA = ventriculoatrial; VJ = ventriculojugular; VP = ventriculoperitoneal; — = not reported.

pressed TSH release, thyroid hormone replacement therapy was reduced by one-half. After a course of estrogen (1.25 mg daily) on Days 1 to 25 and medroxyprogesterone acetate (Provera) (10 mg daily) on Days 16 to 25, she had normal breakthrough bleeding, indicating a physiological uterine response. She was diagnosed with functional hypothalamic amenorrhea, presumed to be due to dieting and frequent, vigorous exercise.

To understand better the cause of her hypothalamic amenorrhea, in November 1993 the patient underwent a LH pulse analysis. Serum samples were obtained every 15 minutes to determine LH concentrations. This provided an indirect measurement of the pulsatility of hypothalamic gonadotropin releasing hormone (GnRH) release. The LH pulse analysis (Fig. 1), which is discussed later, showed reduced LH pulse frequency and was consistent with the diagnosis of hypothalamic amenorrhea. It showed only a single significant LH pulse over 24 hours, which had an amplitude of 3.5 IU/L and occurred 90 minutes after all lights were turned out. The patient was counseled to alter her diet and exercise and was started on an estradiol transdermal release patch.

In December 1993, the patient had a single generalized tonic-clonic seizure. She also reported experiencing six episodes of staring and disorientation during the previous summer, each lasting 15 to 20 seconds. On neurological examination she was globally hyperreflexive and had left-sided Hoffmann’s sign and an abnormal Babinski response. The remainder of the examination was normal. For seizure prophylaxis the patient was given phenytoin, which was soon switched to carbamazepine because of an allergic reaction. An electroencephalogram was obtained, which was consistent with a left frontotemporal seizure focus. A brain magnetic resonance (MR) image with gadolinium contrast enhancement revealed marked dilatation of both lateral ventricles and the third ventricle, with a normal sized fourth ventricle (Fig. 2). There was also no observed flow void in the aqueduct, suggesting cerebral aqueductal stenosis as the cause of noncommunicating hydrocephalus. No other lesion was noted, however, and the cause of the single seizure remained unclear. Funduscopic examination revealed mild papilledema with no visible optic cup and no venous pulsations in either eye, although there was no pallor or hyperemia. Visual field testing using Humphrey perimetry revealed both an enlarged blind spot in each eye and progressive superior and superotemporal loss of peripheral vision bilaterally.

Operation and Postoperative Course. Ten months later the patient elected to undergo treatment of her hydrocephalus by cerebrospinal fluid diversion via an endoscopic third ventriculocisternostomy performed by one of the authors (P.D.A.). Postoperatively she complained of intermittent headaches and mild lightheadedness that resolved completely 6 weeks following surgery. A follow-up brain MR image obtained 4 months postoperatively revealed a flow artifact through the patent ventriculocisternostomy as well as decreased ventricular size (Fig. 3). Six months postoperatively a marked improvement in peripheral vision was noted by the patient and also by repeated Humphrey perimetry. As she had experienced no further seizures, the carbamazepine was successfully discontinued 6 months postoperatively.

Although still below normal, concentrations of FSH (7.6 IU/L), LH (5.2 IU/L), and progesterone (0.1 ng/ml) were increased 4 months postoperatively, and the patient’s estradiol concentration (45 pg/ml) was measurable for the first time. She began to have vaginal spotting 2 months later, and 8 months following surgery experienced her first spontaneous normal menstruation in 13 years. Postoperatively, her D21 progesterone level (5.8 ng/ml) was con-
Sistent with ovulation. She continues to be eumenorrheic 16 months following surgery.

**Discussion**

**Luteinizing Hormone Pulse Analysis**

The diagnosis of hypothalamic amenorrhea is one of exclusion, which is made after ruling out uterine, ovarian, and pituitary disease, as was done in this case. An LH pulse analysis evaluation can be confirmatory. Luteinizing hormone pulse analysis, which requires frequent serum sampling over 24 hours to determine LH concentration, is thought to demonstrate indirectly the pulsatility of hypothalamic release of GnRH into the pituitary portal circulation, direct sampling of which is technically difficult and has not been done in humans. Gonadal function depends on gonadotropic pulses with normal frequency and amplitude, as has been demonstrated in several recent human studies. Dependence of gonadotropin release on a normally functioning hypothalamic GnRH pulse generator is especially suggested in one of these studies by the normal LH release by amenorrheic women to exogenous-ly administered GnRH.

The LH pulse pattern has been thought to discern between organic and functional hypothalamic dysfunction. The nocturnal sleep-related increase in LH pulsatility seen in this patient is also typical of early puberty and can be seen in adult anorexics, in whom the hypothalamic pituitary axis is disrupted. Typically, women with functional hypothalamic amenorrhea will have zero to eight LH surges daily, with eumenorrheic patients demonstrating five to 18 daily surges. The nocturnal LH surge pattern seen in this case is thought to reflect partial hypothalamic functioning.

**Hydrocephalus and Amenorrhea**

Chronic hydrocephalus typically presents in the adult with visual disturbances, papilledema, dementia, or ataxia and only rarely with endocrinological disturbances. Especially unusual is the presentation of secondary amenorrhea as the chief complaint, as this has been reported only once before. Amenorrhea is one of several conditions found in patients who have endocrinological disturbances associated with hydrocephalus. Marked new onset obesity may be found in such patients as well as diabetes insipidus, growth retardation, delayed sexual maturation, precocious puberty, hypothyroidism, or hypoglycemia (from a deficit in growth hormone).

Several mechanisms linking hydrocephalus with amenorrhea have been proposed. Although present in only a minority of patients described in the literature, the empty sella turcica syndrome offers an explanation for some cases. As suggested by Kulali, either chronic or frequent, intermittent elevations of intracranial pressure may lead to a remodeling of the pituitary or the sella itself, giving the appearance of an empty sella. Pituitary compression, however, would not explain the response to GnRH boluses occasionally seen, a response that depends on normal LH and FSH release from the adenohypophysis. In these patients, compression higher in the hypothalamic–adenohypophyseal axis at the level of the portal system may be responsible.

In 1969, Kim, were the first to suggest that pressure in different areas of the hypothalamic–pituitary axis could possibly result in “diametrically opposite phenomena,” delayed sexual maturation or precocious puberty, both of which had been reported with hydrocephalus. Compression at the level of the hypothalamus was suggested in a case presented by Jawadi.
Secondary amenorrhea and hydrocephalus

GnRH release. Under normal puberty, a process also dependent on women who present with primary hydrocephalus have rect, this theory of relative deficiency explains why most lack of priming.26,34

It is possible that noncommunicating hydrocephalus leads to amenorrhea by dilation of the third ventricle and distention of the periventricular and medial basal regions of the hypothalamus, where one finds the ventromedial and arcuate nuclei in which GnRH producing parvocellular neurons are located. If progressive third ventricular dilation is responsible, perhaps GnRH release is disrupted only in the ventral hypothalamus, without disturbance of GnRH production elsewhere, leading to a relative GnRH deficiency. The last GnRH-producing cells to exhibit normal physiology could be those of the median eminence, which is found in the proximal hypophyseal stalk, a location less susceptible to compression from third ventricular expansion. First proposed by Coenegracht, et al.,9 if correct, this theory of relative deficiency explains why most women who present with primary hydrocephalus have undergone normal puberty, a process also dependent on GnRH release.

Hypothalamic Gonadotropin Regulation

The periodicity of GnRH release from the hypothalamus results in a pulsatile LH release with an amplitude four to 10 times the baseline concentration and with a frequency that varies with the menstrual cycle. An LH pulse normally occurs once every 90 minutes in the follicular phase and once every 2 to 4 hours in the luteal phase, much more frequently than the single pulse observed over 24 hours in the patient presented.14

Gonadotropin releasing hormone–producing neurons are located in the periventricular, ventromedial, tuberal, and arcuate nuclei of the hypothalamus. Immunohistochemical analysis in humans has been used to localize these neurons throughout the median eminence as well.3 Moreover, GnRH is not solely released into the pituitary portal system, but is also found to act as a neurotransmitter, being released from the presynaptic terminals of axons that travel through the pituitary stalk to the neurohypophysis. Although it is observed that most GnRH released in the neurohypophysis is found in axons adjacent to the adenohypophysis, the function of GnRH in these neurons is not understood, although regulation of gonadotropin release via an alternative pathway has been suggested.2,32

Endoscopic Ventriculocisternostomy

For treatment of her hydrocephalus, the patient underwent an endoscopic third ventriculocisternostomy, the first performed in a patient presenting with amenorrhea and hydrocephalus. This procedure, when successful, requires no shunting device, sparing the patient the risks of infection and mechanical failure known to occur with implanted systems. Initially described in 197837 for patients with aqueductal stenosis, the ventriculocisternostomy remains functional in 85% to 94% of patients in studies with a mean follow up exceeding 2 years.11,19,21,28 This procedure also does not preclude either repeated ventriculocisternostomy or the subsequent implantation of a ventriculoperitoneal shunt should failure occur.

Conclusions

We present an unusual case of secondary amenorrhea caused by hydrocephalus due to cerebral aqueductal stenosis. As this case demonstrates, the presence of hypothalamic pathology should always be considered in the workup of a woman who presents with amenorrhea. Given the history of weight reduction and vigorous exercise, both common causes of hypothalamic amenorrhea,13 the etiology in this patient seemed clear. Not until a single seizure prompted ordering a brain MR image was the aqueductal stenosis revealed in this patient. Although neu-
roimaging studies should be considered in any patient confirmed to have hypothalamic amenorrhea, we recommend doing so in all patients with normal or low levels of cortisol, as hypercortisolemia correlates with functional amenorrhea.4

References

30. Pollack LJ: Chronic hydrocephalus with dyspituitarism. Inst Quart 4:67, 1913

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