Multiple Sclerosis

Multiple sclerosis is a chronic disease characterized physiologically by the presence of numerous areas of demyelinization in the central nervous system, and clinically, by a variety of neurologic signs and symptoms which have a tendency toward remission and exacerbation. It is primarily a disease of the young adult. The most common symptoms in multiple sclerosis are weakness and paresthesias. Vertigo is the presenting symptom of this disease in 7-10% of the patients and it eventually appears during the course of the disease in up to one-third of the cases. Deafness, on the other hand, is rare, while involvement of the extraocular muscles gives diplopia. Nystagmus is present in about 70% of all cases of multiple sclerosis. The nystagmus, most commonly of the horizontal type, is observed only on lateral gaze. Vertical nystagmus is present in about 33% of the cases. While oscillopsia (rapid oscillations of the eyes in the horizontal plane) is occasionally seen, internuclear ophthalmoplegia is a common ocular manifestation of this disease. In internuclear ophthalmoplegia, the internal recuts on one side is paralyzed while the external rectus on the opposite side is weak, thus producing nystagmoid jerks of the outwardly deviating eye (monocular nystagmus or ataxic nystagmus). Internuclear ophthalmoplegia rarely occurs in other disease, hence its presence is pathognomonic of multiple sclerosis.

Multiple sclerosis has an inherited predisposition although not inherited according to mendelian laws.

Charcot's triad in multiple sclerosis includes nystagmus, scanning speech, and intention tremor.

Myasthenia Gravis

Myasthenia gravis is a disease characterized by weakness and abnormal fatigability of the striated muscles. Its pathophysiology is believed to be impaired transmission across the myoneural junction. The usual age of involvement varies from 5-40 years of age. Children born of a myasthenia gravis mother have neonatal myasthenia gravis symptoms. Their chief symptom is an inability to suck and swallow. The cricopharyngeus muscle, which is not involved in poliomyelitis, is involved in myasthenia gravis. Like multiple sclerosis, remissions and exacerbations are characteristic of this disease. Ocular muscle involvement is present in 40% of the cases. Facial, laryngeal, and pharyngeal muscles often are involved. A distinctive trait of this disease is that the weakness is greatest after exercise and at the end of the day. Nystagmus and vertigo seldom occur.

The diagnosis is made from the patient's medical history together with the neostigmine (Prostigmin or Tensilon) test.
Tensilon (Edrophonium Chloride, PDR, 1981).

Tensilon is a short and rapid-acting cholinergic drug. Chemically, edrophonium chloride is ethyl (m-hydroxyphenyl)-dimethylammonium chloride.

10-mL vials: Each milliliter contains, in a sterile solution, 10 mg edrophonium chloride compounded with 0.45% phenol and 0.2% sodium sulfite as preservatives, buffered with sodium citrate and citric acid, and pH adjusted to approximately 5.4.

1-mL ampules: Each milliliter contains, in a sterile solution, 10 mg edrophonium chloride compounded with 0.2% sodium sulfite, buffered with sodium citrate and citric acid, and pH adjusted to approximately 5.4.

Actions: Tensilon is an anticholinesterase drug. Its pharmacologic action is due primarily to the inhibition or inactivation of acetylcholinesterase at sites of cholinergic transmission. Its effect is manifest within 30-60 seconds after injection and lasts an average of 10 minutes.

Indications: Tensilon is recommended for the differential diagnosis of myasthenia gravis and as an adjunct in the evaluation of treatment requirements in this disease. It may also be used for evaluating emergency treatment in myasthenic crises. Because of its brief duration of action, it is not recommended for maintenance therapy in myasthenia gravis.

Tensilon is also useful whenever a curare antagonist is needed to reverse the neuromuscular block produced by curare, tubocurarine, gallamine triethiodide, or dimethyl-tubocurarine. It is not effective against decamethonium bromide and succinyl-choline chloride. It may be used adjunctively in the treatment of respiratory depression caused by curare overdosage.

Contraindications: Known hypersensitivity to anticholinesterase agents; intestinal and urinary obstructions of mechanical type.

Warnings: Whenever anticholinesterase drugs are used for testing, a syringe containing 1 mg of atropine sulfate should be immediately available to be given in aliquots intravenously to counteract severe cholinergic reactions which may occur in the hypersensitive individual, where he is normal or myasthenic. Tensilon should be used with caution in patients with bronchial asthma or cardiac dysrhythmias.

Dosage

Intravenous Dosage (Adults): A tuberculin syringe containing 1 mL (10 mg) of Tensilon is prepared with an intravenous needle, and 0.2 mL (2 mg) is injected intravenously within 15-30 seconds. The needle is left in situ. Only if no reaction occurs after 45 seconds is the remaining 0.8 mL (8 mg) injected. If a cholinergic reaction (muscarinic side effects, skeletal muscle fasciculations, and increased muscle weakness) occurs after injection of 0.2 mL (2 mg), the test is discontinued and atropine sulfate 0.4 mg to 0.5 mg is administered intravenously. After one-half hour the test may be repeated.
Intramuscular dosage (Adults): In adults with inaccessible veins, dosage for intramuscular injections is 1 mL (10 mg) of Tensilon. Subjects who demonstrate hyperreactivity to this injection (cholinergic reaction) should be retested after one-half hour with 0.2 mL (2 mg) of Tensilon intramuscularly to rule out false-negative reactions.

Dosage (Children): The intravenous testing dose of Tensilon in children weighing up to 75 lb is 0.1 mL (1 mg); above this weight, the dose is 0.2 mL (2 mg). If there is no response after 45 seconds, it may be titrated up to 0.5 mL (5 mg) in children under 75 lb, given in increments of 0.1 mL (1 mg) every 30-45 seconds and up to 1 mL (10 mg) in heavier children. In infants, the recommended dose is 0.05 mL (0.5 mg). Because of technical difficulty with intravenous injection in children, the intramuscular route may be used. In children weighing up to 75 lb, 0.2 mL (2 mg) is injected intramuscularly. In children weighing more than 75 lb, 0.5 mL (5 mg) is injected intramuscularly. All signs which would appear with the intravenous test appear with the intramuscular test except that there is a delay of 2-10 minutes before a reaction is noted.

Tensilon Test for Evaluation of Treatment Requirements in Myasthenia Gravis: The recommended dose is 0.1 mL to 0.2 mL (1 mg to 2 mg) of Tensilon, administered intravenously 1 hour after oral intake of the drug being used in treatment. Response will be myasthenic in the undertreated patient, adequate in the controlled patient, and cholinergic in the overtreated patient.

Migraine Headache

Migraine headache can take various forms. It is usually severe, periodic, unilateral, and lasts for hours. The patient is free of headache between attacks. There is familial tendency with onset at adolescence and prevalence in females.

The headache can be localized at the temporal, retro-orbital, or frontal region. It is preceded by an aura, usually visual. Associated with the headache, the patient may have photophobia, pallor, dizziness, tinnitus, paresthesias, nausea, vomiting, and diarrhea.

It is believed that the etiology is "vascular" and the symptoms precipitated or aggravated by stress. Ergotamine tartarate (Cafergot) has been used to treat the attacks, while methysergide maleate (Sansert) is used for the prevention or reduction of their intensity and frequency. However, Sansert has been reported to cause severe complications, i.e. retrolental fibrosis, pleuropulmonary fibrosis, and cardiac complications.

Cluster Headaches

Histamine Cephalgia, Horton's Syndrome, Nasociliary Neuralgia)

Cluster headaches are typified by bouts of attacks for a few days between months or years of remission. It often occurs in young adults. The headache is severe, unilateral, lasts less than an hour, and often awakes the patient from a sound sleep. It may be associated with scleral injection, lacrimation, ipsilateral rhinorrhea, and nasal congestion. The treatment is similar to that for migraine headache.
Temporal Arteritis

Temporal arteritis mainly strikes those in their 50s and 60s. Its pathology is similar to that of periarteritis nodosa except for a more severe inflammatory reaction around the vessels and for the presence of many multinucleated giant cells in the media (giant cell arteritis). It usually is restricted to the temporal arteries.

The patient suffers severe pain along the arteries, feels lethargic, and has a low-grade fever. Temporal arteritis is usually a self-limiting disease unless the central artery of the retina is involved in which case residual blindness would be present. The treatment for this disease consists of steroid administration.

Sarcoidosis

Sarcoidosis is a multifaceted disease of unknown etiology. Pathologically, epitheloid cell tubercles are found without evidence of necrosis or caseation. Giant cells containing calcified bodies are identified in these tubercles. The usual age of onset is between 20-50 years old. The organs possibly involved, in order of decreasing frequency, are the lymph nodes, lungs, skin, eyes, and bones. In the practice of otolaryngology, the nose, tonsil, and larynx are sites of predilection. Localization of sarcoidosis in the respiratory tract and in the salivary gland happens in only about 3% of all cases. The most common ophthalmic manifestations are iridocyclitis, keratitis, conjunctivitis, and episcleritis.

Uveoparotid fever of Heerfordt, a variant of sarcoidosis, is characterized by fever, parotid involvement, uveitis, and facial paralysis (usually bilateral and transient).

The frequency of hypercalcemia in sarcoidosis ranges from 3-20%, and for hyperglobulinaemia from 45-70%. Leukopenia is encountered quite frequently while eosinophilia occurs in 20% of the cases.

Pituitary Adenoma

The pituitary gland (hypophysis) has two divisions in the human. The anterior portion of the pituitary is called the adenohypophysis. Prolactin, growth hormone (GH), adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) are among the hormones released by the adenohypophysis. Release of all of these hormones is under the control of hypothalamic factors and/or hormones. The posterior portion of the pituitary gland is termed the neurohypophysis, and releases antidiuretic hormone (ADH or vasopressin) and oxytocin. Both of these hormones are actually formed in the supraoptic and paraventricular nuclei of the hypothalamus, from which they are transported via the portal venous system to the neurohypophysis for storage and ultimate release.

The cell types of the anterior pituitary gland by light microscopy include chromophobe cells (comprising 50% of the total cell population), acidophils (also termed alpha cells; accounting for 40% of the pituitary cells), and basophils (also called beta cells; making up 10% of the pituitary cell population). The glial cells of the neurohypophysis are termed pituicytes. The older method of classifying pituitary adenomas by light microscopy with the
standard hematoxylin-eosin staining - chromophobe, eosinophilic, or basophilic adenoma - is now not adequate in view of current findings through immunohistochemistry, electron microscopy, and serum hormone assays. Pituitary tumours are now classified as functional (hormone-secreting) or non-functional (non-hormone-secreting).

The differential diagnoses of sellar and parasellar lesions include the following:

1. Pituitary adenoma
   a. Functional
      1) Prolactin-secreting - most common.
      2) Growth hormone (GH) secreting.
      3) Adrenocorticotropic (ACTH) secreting.
      4) Other, less common secreting tumors.
   b. Nonfunctional.

2. Invasive, "malignant" pituitary adenoma - less than 3% of cases.

3. Pituitary apoplexy.


5. Cranipharyngioma.

6. Metastatic neoplasms: breast, lung, prostate, etc.

7. Hypothalamus
   a. Optic and/or hypothalamic glioma.
   b. Hamartoma of the hypothalamus.

8. Epidermoid, dermoid, germinoma.

9. Chordoma, chondrosarcoma, osteochondroma.


11. Aneurysm.

12. Empty sella syndrome: may be primary or secondary, with or without enlarged third ventricle.
13. Inflammatory

a. Sellar abscess.

b. Mucocele of sphenoid sinus.

c. Granulomatous disease: sarcoidosis, tuberculosis.

Signs and symptoms of pituitary tumors may be placed into three groups:

**Endocrine**

**Functional Tumours**

Prolactinoma. This is the most common pituitary tumor. It is most frequently seen in young females; prolactinomas present with galactorrhea with or without amenorrhoea. The majority are microadenomas (10 mm or less in diameter). By light microscopy, most of these tumors are chromophobe adenomas.

Growth Hormone (GH) Secreting Adenomas. Gigantism may be seen in childhood cases before the epiphyses of the long bones have been closed. Acromegaly is seen in adults. Classically, these tumors were described as eosinophilic adenomas. However, most cases are chromophobe adenomas by light microscopy. Growth hormone secreting tumors are the second most common of the endocrine active adenomas.

Adrenocorticotropic (ACTH) Secreting Adenomas. These present clinically as Cushing's disease. These tumors are usually microadenomas, and occur much less frequently than prolactinomas and growth hormone secreting tumors. They are more common symptomatically in females. Hyperpigmentation with increasing sellar size may be seen in Cushing's syndrome after bilateral adrenalectomy, and is known as Nelson's syndrome. ACTH-secreting tumors of Nelson's syndrome tend to be more aggressive and larger in size. Basophilic adenomas are usually demonstrated by light microscopy and hematoxylin-eosin staining techniques.

**Nonfunctional Tumors**

These neoplasms may present without endocrine deficiencies, or may present with decreased function of one or more hormones. In its most severe form, panhypopituitarism with visual symptoms with or without signs of increased intracranial pressure and/or extraocular muscle palsies may be seen.

**Pituitary Adenomas**

These tumors may occur as part of the syndrome of multiple endocrine adenomatosis. The majority of cases of Wermer's syndrome (multiple endocrine adenomatosis type I) are associated with pituitary tumors, as well as parathyroid, pancreas, adrenal, and/or thyroid tumors.
Visual Symptoms and Signs

The classic visual finding associated with enlarging suprasellar extension of pituitary adenomas is bitemporal hemianopsia associated with a progressive decrease in visual acuity.

If there is significant lateral extension of tumor growth toward the cavernous sinus, extraocular muscle palsies (cranial nerves III, IV, and/or VI) may be noted.

The syndrome of pituitary apoplexy may occasionally be seen in pituitary tumors. There is a sudden loss of vision associated with hemorrhage within a pituitary adenoma. Severe headache, decrease in level of sensorium, extraocular muscle palsies, and meningismus also may occur. Pituitary apoplexy is a relative emergency which particularly lends itself toward a transsphenoidal approach for removal of the hematom if a patient with this syndrome is seen relatively soon after the apoplectic episode.

Headache

Headache is a common symptom associated with pituitary adenomas. Initially, the headache may be due to pressure caused by growth of the tumor along the dural covering of the cavernous sinus and/or stretching of the dura of the diaphragm sellae. With further suprasellar extension of tumor, obstruction of the foramina of Monro may occur with associated hydrocephalus and increased intracranial pressure. This is usually a late development. Pituitary adenomas with only headache as a symptom usually are not diagnosed because headache is such a common, nonspecific symptom.

Diagnosis

Today, most functional pituitary adenomas are diagnosed as intrasellar lesions without signs of mass effect. Most endocrine inactive, nonfunctional tumors are not diagnosed until signs and symptoms of hypopituitarism or mass effect evolve. An asymptomatic enlarged sella turcica is occasionally noted on skull or sinus x-rays.

Transseptal, Transsphenoidal Approach to the Sella Turcica

Anatomically, the important features in regard to the sella turcica include the following:

1. Inferiorly, there is a dural covering over the pituitary gland.

2. Superiorly, the diaphragm sellae, through which the infundibulum of the pituitary passes, is located.

3. Anteriorly, the venous circular sinus is located within the dura.

4. Posteriorly, the dorsum sellae may be palpated on intrasellar exploration.

5. Located on either side laterally is the venous cavernous sinus, which contains the third, fourth, and sixth cranial nerves, as well as the first and second divisions of the fifth
cranial nerve, and the internal carotid artery.

**Preoperative Evaluation of Pituitary Tumors**

The team approach is essential in evaluation of lesions in and adjacent to the pituitary gland. This should include the following:

1. Complete otolaryngologic evaluation, including examination of gums and teeth.
2. Complete neurologic examination.
4. Endocrinologic workup (as indicated below).
5. Neuroradiologic evaluation, including:
   a. Skull x-rays.
   b. Polytomography of the sphenoid sinus and sella turcica, including submentovertex views.
   c. Computed tomography scan.
   d. Arteriography - especially digital venous angiography - may be required for localization of the cavernous portion of the internal carotid artery, localization of the A-1 segment of the anterior cerebral artery, and/or to rule out an aneurysm.
   e. Pneumoencephalography today is only rarely required.
6. Nose and throat culture and sensitivity.
7. Antibiotics as indicated. Usually penicillin is used, unless the preoperative nose and throat culture indicates a resistant organism, in which case an appropriate antibiotic according to sensitivity testing is used.
8. Preoperative and intraoperative steroids with continuance into the postoperative period.

**Preoperative Endocrine Studies for Pituitary Adenomas**

Complete endocrinologic evaluation is required for evaluation of pituitary adenomas. Endocrine studies should include serum cortisol (A.M. and P.M.), growth hormone (with concomitant serum glucose), prolactin, complete thyroid evaluation (including T3 uptake, T4, free T4), FSH, LH, and serum and urine electrolytes and osmolalities. In addition, further tests such as insulin tolerance test (ITT), TRH stimulation, and glucose tolerance test (GTT) may be required. The normal values for these tests vary from laboratory to laboratory.
Postoperative Endocrine Care

Most cases undergoing pituitary surgery will have at least a transient diabetes insipidus. In a few cases this may be permanent, especially in cases undergoing total hypophysectomy for metastatic carcinoma of the breast. Hourly monitoring of urine output and specific gravity is required in the immediate postoperative period. In addition, close monitoring of serum and urine electrolytes and osmolalities is required. Acutely, one may assume that the patient has diabetes insipidus if there is prolonged urine output of greater than 250 mL/hr with a specific gravity of 1.005 or less. Therapy may initially include intravenous fluids at a rate to replace the previous hour's urinary output. However, if the volume of urinary output becomes too excessive and/or prolonged, one may give vasopressin (Pitressin). There are two types, as in-oil preparation and aqueous Pitressin. The latter has a shorter duration of action than the former and, in general, is preferred as the initial mode of therapy for diabetes insipidus if fluid replacement is not effective. In cases of chronic diabetes insipidus, intranasal desmopressin acetate (a synthetic analogue of vasopressin) may be required. Steroid and thyroid maintenance therapy may be required, especially in cases of preoperative panhypopituitarism. In such instances a total of 37.5 mg of cortisone acetate and 2 gr of dessicated thyroid, or its equivalent (such as levothyroxine sodium 0.1-0.2 mg), each day will be sufficient. This dosage is required in hypophysectomy cases and in instances of pituitary adenoma presenting with hypopituitary function.

Rationale for Hypophysectomy in Patients with Carcinoma of the Breast

The indications for hypophysectomy in cases of carcinoma of the breast include that of (1) advanced disease with evidence of a previous objective response to endocrine manipulation and (2) intractable bone pain. If estrogen-binding factor is present in tumor tissue in appropriate cases, the chance for an objective response to hypophysectomy is greatly enhanced.

Differential Diagnosis of Cerebellopontine Angle Tumours

Acoustic Neuroma

Hearing loss (retrocochlear pattern) is an early symptom, usually associated with tinnitus. With a progressive increase in tumor size, involvement of the fifth (decreased corneal reflex, facial hypesthesia) and seventh (peripheral facial paresis) cranial nerves occurs. Further tumor growth may involve the cerebellum (gait ataxia, dysmetria, nystagmus, etc), brain stem (hemiparesis, Babinski's response, etc), and/or jugular foramen (ninth, tenth, and eleventh cranial nerves). Bilateral acoustic neuromas may be seen in von Recklinghausen's disease.

X-rays, including skull films, Stenvers' views and polytomography of the internal auditory meatus usually reveal enlargement of this structure. Computed tomography (CT) scanning is positive in most larger tumors (greater than 1 cm in diameter) in the cerebellopontine angle. These tumors tend to be clearly demarcated masses whose tissue density may be close to neural tissue. Usually, significant contrast enhancement is present. Smaller lesions, including some intracanalicular acoustic neuromas, may be seen on more recent CT scanners, such as the GE model 8800. Computer tomography scanning has antiquated the use of older studies, such as brain scanning and pneumoencephalography.
Cerebellopontine angle myelography is indicated for smaller lesions - particularly intracanalicular lesions - even if CT scanning is negative, if an appropriate history and clinical findings (including audiometry) are suggestive of an acoustic neuroma. In such cases, nonfilling of the internal auditory meatus and/or outlining of an intracanalicular lesion are noted. Cerebrospinal fluid protein often is elevated. Either metrizimide or Pantopaque may be used as a contrast media. Metrizamide has the advantage of being water soluble (and thus does not have to be removed at the end of the procedure) and also may be used with concomitant CT scanning for brain stem and/or cerebellopontine angle cisternography evaluation. Headache, nausea, and vomiting are the most common side effects of metrizamide. Seizures are also a risk with metrizamide, and this dye should not be used in patients with a past history of seizure disorder or patients who are on phenothiazines.

Angiography may reveal displacement of the anterior inferior cerebellar artery and/or petrosal vein, as well as other vascular displacement in larger tumors.

**Meningioma**

This is the second most common primary cerebellopontine angle mass lesion. Hearing loss tends to occur later in the clinical course of these lesions as compared with acoustic neuromas. Multiple cranial nerve palsies, brain stem, and cerebellar signs may be present with further tumor growth.

X-rays may reveal abnormal calcification and/or local hyperostosis involving the petrous ridge, but the internal auditory meatus will be normal in size.

Computed tomography scanning is nearly always positive in these lesions, exhibiting significant contrast enhancement.

Cerebellopontine angle myelography, if performed, reveals nonfilling of the cerebellopontine angle.

Angiography will reveal local vessel displacement. Tumor stain also may be seen (usually not present in acoustic neuromas).

**Epidermoid**

This is the third most common primary cerebellopontine angle mass lesion. Hearing loss, if present, tends to occur late in the patient's clinical course. Multiple cranial nerve palsies, with or without brain stem and/or cerebellar signs, may be found.

Plain skull films and laminagrams are usually within normal limits. The internal auditory meatus is normal in size.

Computed tomography scanning may reveal a low-density lesion in the region of the cerebellopontine angle which does not exhibit contrast enhancement.

Cerebellopontine angle myelography, if performed, reveals an irregular angle mass lesion with contrast material irregularly filling the interstices of the tumor.
Pneumoencephalography usually is not performed currently. If performed, this study may be diagnostic, revealing air filling the fingerlike interstices of an angle mass lesion. Cerebrospinal fluid protein may be elevated.

Angiography may reveal local vascular displacement without tumor stain.

**Metastatic Neoplasm**

Metastatic tumors (lung, breast, etc) have a more rapid clinical course than the first three diagnostic possibilities. Multiple, bilateral lower (and upper) cranial nerve palsies usually evolve as a manifestation of meningeal carcinomatosis. Most often a previous history of neoplasia is obtained. Evidence of metastatic disease elsewhere often is present. Plain skull films and polytomography of the internal auditory meatus are normal.

Computed tomography scanning is usually positive with contrast enhancement in larger lesions. Multiple lesions elsewhere intracranially may be diagnosed. In the initial phase of meningeal carcinomatosis, the CT scan may be negative.

Cerebellopontine angle myelography usually is not performed. Cerebrospinal fluid protein may be elevated and tumor cells may be noted on cerebrospinal fluid cell cytology analysis.

Angiography usually is not required. If it is performed, local vascular displacement with or without a tumor stain may be noted.

**Glioma**

Occasionally brain stem or cerebellar gliomas (astrocytoma, subependymoma, etc) may "escape" into the subarachnoid space and grow out toward the cerebellopontine angle. Such patients may present with symptoms of a lesion in this area. Examination may reveal a predominantly brain stem or cerebellar lesion. Plain x-rays are usually normal.

Computed tomography usually will reveal a cerebellar and/or brain stem glioma. Contrast enhancement is commonly seen. Metrizamide cisternography with CT scanning may be quite helpful in revealing brain steam asymmetry in questionable brain stem lesions. Angiography may reveal local vascular displacement, with or without a tumor stain. Despite the above noted findings, on occasion the diagnosis may be unsuspected and made only at the time of surgery.

**Aneurysms and Other Lesions**

Aneurysms, if large enough, may be suggested on CT scanning. The definitive diagnosis is made by angiography. Chordoma and other bony lesions may be diagnosed by appropriate x-rays, including polytomography, and CT scanning. Angiography may reveal an avascular mass.
Miscellaneous

1. Parosmia: perverted sense of smell.
   Hyperosmia: oversensitive sense of smell.
   Hyposmia: impaired sense of smell.
   Anosmia: total loss of smell.
   Cacosmia: a sense of foul smell when none is present.

2. Diphenylhydantoin (Dilantin) and carbamazepine (Tegretol) have been used to treat trigeminal neuralgia.

3. Vitamin A has been used to treat anosmia (see Chap. 14).

4. Ammonia stimulates cranial nerve V and not the cranial nerve I. Hence, it can be used when a psychogenic cause of anosmia is suspected.