Porphyria

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Introduction:

Medical literature of recent years has demonstrated a crescendo in reporting of an acute condition mimicing an acute surgical emergency with the classical triad (1) abdominal pain, (2) peripheral neuropathy (3) emotional changes. These articles have resulted in an increase in the "index of suspicion". Since 1949 several cases have been diagnosed in Nova Scotia. The rarity of this condition in older literature was probably due to failure in its recognition. The purpose of this article is four fold: (1) To arouse a clinical suspicion that will ultimately lead to proper diagnosis, (2) to protect the patients from unnecessary surgical procedures which have served in the past to add another pain to the already painful abdomen and give an additional abdominal scar, (3) to prevent the use of drugs that might precipitate exacerbations of the disease, (4) to advocate honest trial of one of the non-specific therapeutic agents that has on occasions brought the patients some relief.

Nomenclature and Classification:

The confusion that has arisen concerning the nomenclature of the disease may be explained at this point. Hoppe-Seyler[1] gave the name "hematoporphyrin" to a complex pigment which was formed by the action of a strong sulphuric acid on hemoglobin. Subsequent investigations found in deeply pigmented urine a substance which gave the same absorption spectrum as hematoporphyrin. Gunther[2] in his early reports suggested that this substance might not be identical with Hoppe-Seyler's hematoporphyrin. In 1911 Gunther reviewed all the the reports on patients who excreted large amounts of this pigment in their urine. On the basis of his analysis of the material in these scattered publications he concluded that porphyrinuria was a physiological process of little importance in the disease status and an essential symptom of a rare disturbance in pigment metabolism of constitutional origin. He then named this constitutional anomaly of pigment metabolism "hematoporphyria" instead of the more correct "porphyria" as demonstrated by subsequent investigators.

Mason et al[3] use the term "hematoporphyrinuria" to signify the excretion of any porphyrin in the normal as well as the diseased states, and the term "hematoporphyria" for a specific disease of pigment metabolism in which the pigments excreted in the urine are uroporphyrin and coproporphyrin but never hematoporphyrin as prepared by Hoppe-Seyler.

Markovitz[4] used the term porphyrinuria to denote any condition in which an excess of coproporphyrin or uroporphyrin or both is found in the urine. This includes not only the disease porphyria but also many other conditions in which abnormal amounts of corproporphyrin are excreated in the urine.

The disease porphyria is thought to be a constitutional defect leading to a disturbance in the metabolism of pyrroles, which in turn results in excretion of abnormal types and amounts of porphyrins in the urine.

Watson and co-workers[5] propose the following classifications, based upon their concept of the site of origin of the abnormal porphyrins.

(1) Porphyria erythropoietica - indicating that porphyrins are found in large amounts in the bone marrow. There is red staining of the teeth and bones, photosensitivity and splenomegaly.

(2) Porphyria hepatica - suggests the liver as the site of formation of abnormal types and excessive amounts of porphyrins.

(a) Acute intermittent porphyria - the most common porphyria.

(b) Mixed porphyria which is distinguished from the acute on the basis of its photosensitivity.

Symptoms and Signs:

Gastro intestinal Symptoms: Severe, colicky abdominal pain was the major gastrointestinal symptom. Physical findings, do not support the diagnosis of a surgical emergency. The patients complain of tenderness on palpation, but the abdomen is soft and there is no rebound tenderness.

Nausea and vomiting may accompany the bouts of pain. A considerable number have constipation.

Peripheral Neuropathy: Motor symptoms which varies from weakness to quadriplegia occurred in 75% of cases. There may be loss of deep tendon reflexes. The muscular pain is often described as burning or aching in character and may be the chief complaints.

Emotional Changes: Nearly all the patients display emotional changes from irritability, tiredness or restlessness to psychic changes such as hallucinations, delusions, delirium, confusion, and epileptic seizures.

Cranial Nerve Involvement: Varies from mild vocal paresis to respiratory failure and death. A high pitched whining voice is a striking feature in a high percentage of patients.

Vital Changes: Hypertension (150 /100 mm. of Hg.) in a number of patients. About the same number have tachycardia. Fever is usually of a low grade when it occurs. Brown pigmentation of the skin may occur in some patients. Jaundice has also been reported to have occurred.

Laboratory findings: A considerable number of patients have port wine colored urine, others have normal colored urine which darkens upon standing. The Watson-Schwartz test for porphobilinogen is positive in almost 80% of the patients. In the remainder uroporphyrin can be demonstrated.

Blood: A leucocytosis of 10,000 to 31,000 has occurred in about one-third of the patients. N.P.N. was elevated in two-thirds of the patients.

Diagnosis:

Acute intermittent porphyria has been mistakenly diagnosed combat fatigue, pheochromocytoma, appendicitis, glomerulo-nephritis, Addison's disease, cholecystitis, bowel obstruction, epilepsy, poliomyelitis, muscular

dystrophy, schizophrenial depression and delirium tremens.

To diagnose this disease the index of suspicion must be high. Patients presenting a history of acute abdominal pain with minimal physical findings, a peripheral neuropathy of any type, a continued psychoneurotic condition, or a history of many laparotomies with persisting pain and passing dark red urine should be suggestive enough to carry out the Watson-Schwartz test[6] for porphobilinogen which can be done rapidly as follows: equal parts of Erhlich's reagent and urine is mixed in a test tube. An equal volume of sodium acetate is added to this mixture. A few drops of chloroform are then added and the contents thoroughly mixed. The porphobilinogen being soluble in the chloroform remains in the aqueous whereas urobilinogen of the urine is dissolved in the chloroform layer. It is important to have sodium acetate in the mixture in the above proportions for complete separation of the porphobilinogenaldehyde.

Pathogenesis:

Familial tendency of the disease receives conflicting reports. It does not seem very prevalent among negros. The ratio of females to males is 3 to 2. Seventy per cent of the patients are between 21 to 40 years. Drugs have been incriminated. Barbiturates, sulfonamides, chloroquine, 'Sedormid', arsenic, lead and other heavy metals have been suspected as a cause of acute intermittent porphyria in some reports, but denied as a cause by others. Barbiturates are not now given to patients with acute intermittent porphyria.

The relationships between the pathology metabolites and the symptoms are not clear. Watson[5] injected relatively large amounts of coproporphyrin into human volunteers without creating symptoms.

Porphobilinogen is not found in the urine of patients with porphyria hematopoietica, and these patients do not have the abdominal pain and nervous involvment which is seen in acute intermittent porphyria. Instances have been reported in which patients have no porphobilinogen or uroporphyrin in the urine during the acute exacerbation of the disease, but later in the recovery period, these substances appeared[7].

Porphyrins are excreted as a zinc complex. To rule out excessive loss of zinc as a cause of the symptomatology, Nesbitt[8] measured the zinc content of the livers and pancreas of patients who died of the disease and found it to be normal.

Psychic trauma has been advanced as an etiological factor in this disease[9].

Pathology:

The major findings are in the nervous system and consist of a patchy degeneration of the myelin sheaths of the peripheral nerves, and chromatolysis of the anterior horn cells of the spinal cord. Abbot and Evans[10] noted that myelin degeneration was most severe where the sheaths entered the central gray matter of the cord and in the intracortical portions of the cerebral cortex. Because the blood supply is best in these areas, this suggests to them a toxic factor carried by the blood stream.

Varied changes have been described in the Purkinje cells of the cerebellum, the cells of the dentate nucleus, cerebral cortex, basal ganglion, hypothalamus and cranial ganglion. The extent of these changes are dependent on the duration of the disease.

Necrotic changes in the centrilobular cells of the liver have been reported. The kidney tubules become lined with a red fluorescing material as shown by the ultra violet light.

Treatment:

There is no specific therapy. The Vitamin B complex have been tried since they are a part of the porphyrin-containing enzyme systems. The latest enthusiasm for their use was massive doses of riboflavin. Vitamins C, E, B_{12} and liver extract have been ineffective.

Intravenous procaine for episodes of abdominal pain has been tried with great success.

Calcium salts, because they form insoluble salt with porphyrins, were advocated. Results are discouraging.

Morphine has been useful in relief of pain.

A.C.T.H. seems to be the present form of medication being used.

Several cases are reported in the literature. Some reports are discouraging while others report it to be very effective.

Prognosis:

In the series of 69 patients reported by Markovitz[4], the overall mortality was 58%. The greatest mortality of a single episode is low. The poorest prognosis is among the patients with cranial nerve involvement where the mortality ranges from 60 - 90%.

References:

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