Hereditary Mental Depression and Parkinsonism With Taurine Deficiency

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An unusual neuropsychiatric disorder inherited in autosomal dominant fashion occurred in three successive generations of a family. Symptoms commenced late in the fifth decade in six affected patients and led to death in four to six years. The earliest and most prominent symptom was mental depression not responsive to antidepressant drugs or electroconvulsive therapy. This was accompanied by exhaustion, sleep disturbances, and marked weight loss. Later in the disease, symptoms of parkinsonism appeared, and respiratory failure occurred terminally.

The most recently affected family member was investigated biochemically late in his illness. Concentrations of taurine were greatly diminished in plasma and cerebrospinal fluid, and at autopsy, all regions of brain examined had a markedly reduced taurine content. Since taurine is a putative inhibitory synaptic transmitter, deficiency of brain taurine may possibly have caused the psychiatric and neurological manifestations of this disorder.

(Arch Neurol 32:108-113, 1975)

Some forms of parkinsonism are familial, and for many years, occasional pedigrees have been reported in which this disorder has been inherited in an autosomal dominant fashion. Genetic factors are also generally believed to play a part in the cause of some forms of mental depression. In a survey of the families of patients with unipolar depressive disorders, mental depression was found in at least one of the parents of a quarter of the patients studied.

The incidence of mental depression is substantially higher in patients with parkinsonism than among other hospitalized patients, and the degree of depression appears not to be related to the duration or severity of the Parkinson disease process. However, we have been unable to find any reported pedigrees of depressive illness complicated by parkinsonism that exhibit an autosomal dominant mode of inheritance.

This report describes a "new" neuropsychiatric disorder occurring in three successive generations of a family and characterized by progressive mental depression, parkinsonism, and death within four to six years of the onset of symptoms. The most recently affected member of this family was investigated biochemically, and a marked deficiency of taurine was...
found in his blood, cerebrospinal fluid (CSF), and brain.

**PATIENTS**

**CASE 1.**—The pedigree of the T family is shown in Fig 1. III-3, the proband, enjoyed good health until the age of 50, but thereafter began to withdraw from social situations, lose interest in his family and work, and became continuously depressed. During the second year of his illness, III-3 experienced frequent nausea and vomiting, had difficulty sleeping, and lost considerable weight. During the third and fourth years of his illness, the patient continued to be mentally depressed and complained of constant fatigue. His gait became abnormal, with little movement of arms and shoulders while walking. He also experienced difficulty in judging distance while driving a car and repeatedly narrowly missed rear-end collisions.

When first seen by one of us (P.J.A.B.), four years after the onset of symptoms, III-3 complained of severe fatigue and of gagging on food and showed subtle features of parkinsonism, such as a paucity of facial expression and a tendency to hold his head and trunk stiffly. His ocular movements were normal. There was no abnormality of tone in his extremities, and he showed neither tremor nor bradykinesia. Six months later, he developed a coarse resting tremor of his hands. His face was impassive, and he blinked rarely, but tone remained normal. There was awkwardness of fine finger movements through a small range. Tendon reflexes and plantar responses were normal.

During the last year of his illness, the patient's speech became progressively harder to understand, he had difficulty swallowing, and he had alternating periods of apnea and panting respiration. He complained of exhaustion, was depressed, had nocturnal hallucinations as well as periods of mental confusion, and continued to lose weight. He died unexpectedly of respiratory failure after an illness of six years. Neither the symptoms of parkinsonism nor the depression was altered by treatment with levodopa or amantadine hydrochloride. Results of many laboratory tests throughout the illness were normal, including routine tests of the CSF. The electroencephalogram (EEG) was normal in the early stages of his illness, but subsequently, it became slightly abnormal, with an excess of posterior slow activity bilaterally. Stool examinations showed abnormally large amounts of neutral fat during the last two years of his life. During his terminal illness, arterial Pco2 was repeatedly low, while Pco2 was normal.

**CASE 2.**—III-1, an older brother of the proband, was well until the age of 47. The first symptoms of illness were gradual withdrawal from social activities and complaints of feeling constantly depressed and fatigued. These symptoms were not improved by therapy with antidepressant drugs. In the third year of his illness, he began having severe sleep disorders, with insomnia, nightmares, and sleep walking. He lost weight steadily throughout his illness. Expressionless facies was present by the third year of his illness, and in the fourth year, he failed to swing his arms on walking and exhibited a tremor of the hands. This patient also had unusual difficulties in driving a car, frequently coming too close to stop signs before slowing down.

**Fig 1.**—Pedigree of T family. Numbers under symbols indicate present age or age at death.

III-1 was first hospitalized about a year before his death for investigation of fatigue and weight loss from his usual weight of 67.8 kg (150 lb) down to 51.9 kg (115 lb). Results of extensive gastrointestinal investigations were unremarkable. Subtle features of parkinsonism were observed. On his final hospital admission one year later, III-1 complained of difficulty in breathing unrelated to exertion, as well as of attacks of dizziness and a feeling of falling backward. He was disoriented, and his thinking was slow. He showed an impulsive facies and a rhythmic distal tremor, but had normal tone and reflexes. He failed to swing his arms on walking. He was emaciated, but not weak. During this admission, he suddenly became unresponsive and failed to breathe on his own. A tracheotomy was performed, and the patient was placed on a respirator, but spontaneous respirations were never adequate thereafter, and death due to bronchopneumonia occurred a few weeks later.

**CASE 3.**—III-5, another brother of the proband, enjoyed good health until age 45. He then progressively withdrew from family and friends and became depressed. During the first three years of illness, symptoms were limited to severe mental depression and sleep disturbance, and apparent difficulties in judging distance. He repeatedly drove through stop signs, had two rear-end automobile collisions, and when piloting his fishing boat would misjudge distance and crash into docks. He was admitted several times to psychiatric hospitals, where he was thought to have involuntional melancholia. He was given repeated courses of electroconvulsive therapy, as well as tricyclic antidepressants, but without beneficial effect. In the last three years of illness, he lost a large amount of weight.

On his final hospital admission, III-5 complained of loss of appetite, fatigue, lack of ambition, gagging, and shortness of breath. Examination showed a mask-like facies, slow slurred speech, and tremors of the tongue at rest and of the fingers. Muscle tone was normal, as was power in his extremities. Reflexes, including plantar responses, were normal. Extensive laboratory investigations were noncontributory. These included a normal EEG and CSF normal to routine testing. Without prior warning of observed respiratory inadequacy, III-5 stopped breathing unexpectedly and failed to respond to resuscitation.

**CASE 4.**—II-2, mother of the three affected brothers, enjoyed good health until she was 50. She then withdrew progressively from all social activities, became apathetic, and complained of always being
fatigued. She lost much weight and in the latter half of her illness had great difficulty in breathing. She died four years after the onset of symptoms.

**Case 5.**—II-1, a brother of the mother, became ill at about age 50 with mental depression and fatigue. He lost weight, had difficulty swallowing, and was always gasping for breath. He died five years after the onset of illness and was thought by his physician to have parkinsonism.

**Case 6.**—I-1, father of the preceding two patients and grandfather of the proband, became ill at age 49. He was mentally depressed throughout his illness, had a marked tremor, and toward the end of his illness had difficulties in breathing and swallowing. He died five years after the onset of symptoms.

**Doubtful Cases.**—II-9 became depressed and committed suicide at the age of 42. Further details about this man were unavailable. III-7, a sister of the proband, has been withdrawn, apathetic, and continuously depressed for one year. Neurological examinations have so far shown no abnormalities.

**METHODS**

Plasma amino acid levels were determined on specimens of blood obtained from patients and control subjects after overnight fasting. Analyses were performed with an amino acid analyzer (Technicon), using a lithium citrate elution buffer system. Special precautions were taken to avoid contamination of plasma specimens by taurine and other compounds that are present in high intracellular concentration in leukocytes and platelets.

Amino acids in CSF and urine specimens were similarly analyzed, and CSF specimens were not used if contaminated with red cells or leukocytes.

Samples, limited as far as practical to gray matter, were dissected from several regions of the brain of patient III-3 (case 1) at autopsy 12 hours after death. These samples were weighed and then frozen at −80°C until they could be prepared for analysis. They were homogenized and deproteinized in 0.4 M perchloric acid, with the same procedure we previously described, except that homogenization was carried out in a Teflon-pestle glass tissue grinder. Free amino acids and other ninhydrin-positive compounds were then identified and quantitated with the same amino acid analyzer system used for plasma, CSF, and urine.

**RESULTS**

**Taurine in Plasma and CSF**

Of the three members of the T family who in recent years clearly suffered from depression with parkinsonism, special biochemical studies were carried out only on patient III-3, unfortunately. One week before his death, amino acids were analyzed in his fasting plasma and CSF. The only abnormality encountered was that of an unusually low level of taurine in both fluids (plasma, 0.023 μmol/ml; CSF, 0.10 μmol/100 ml). Mean values were found by the same method in control adults. Control plasma taurine values were all obtained from 75 healthy adults (0.056 ± 0.013 μmol/ml). The control values for CSF taurine were obtained from 56 adults with a variety of neurological disorders (0.64 ± 0.16 μmol/100 ml). None of these patients, however, had any known disorder of sulfur amino acid metabolism, nor increased CSF cell counts.

Patient III-3 had the lowest levels of taurine in his plasma and CSF that we have ever observed in an adult. (Low plasma taurine levels are often found in normal infants.) Because the patient died unexpectedly before the analyses were completed, urine was not collected, and no information is available as to its taurine content. No abnormality of any other sulfur-containing amino acids was detectable in the patient’s plasma or CSF.

**Taurine in Brain**

Thirty-six different amino acids and related compounds were quantitated in six regions of brain obtained at autopsy from patient III-3. All of these, except for taurine, were present in concentrations comparable to those found in autopsied brain of per-
sons dying without neurological or psychiatric disease. The content of taurine, however, was reduced in all regions examined.

The Table shows the taurine content of six areas of III-3's brain as compared with values found in the same areas of the autopsied brains of 11 neurologically normal subjects, 11 patients dying from Huntington chorea, and a single patient dying with severe nonhereditary parkinsonism. Values for the Huntington chorea patients are included in the Table, since they provide the only available data regarding the taurine content of brain affected by a chronic degenerative neurological disorder in which there is no known involvement of this amino acid. The deficiency of taurine in patient III-3's brain was most marked in the cerebellar cortex and least marked in the substantia nigra, among the six regions sampled.

The taurine content of autopsied human brain is similar to that of biopsied human brain, and it is, therefore, reasonable to assume that there was a generalized deficiency of taurine in III-3's brain during life. Contents of methionine, cystine, and of reduced and oxidized glutathione are markedly different in autopsied human brain from those found in living human brain, but the values for these four sulfur-containing amino acids, as well as for cystathionine, appeared unremarkable in patient III-3's brain. No traces were found of S-adenosylhomocysteine, homocystine, cysteinesulfonic acid, cysteic acid, or hypotaurine, other easily measurable sulfur-containing metabolic intermediates between methionine and taurine. We emphasize that the content of γ-aminobutyric acid (GABA) was entirely normal in all examined areas of III-3's brain, in sharp contrast to the low levels of GABA found in the striatum and substantia nigra of patients dying with Huntington chorea.

**Pathological Changes in Brain**

Gross examination of the brain of patient III-3 (case 1) showed nothing abnormal, except for distinct depigmentation of the substantia nigra. Histological abnormalities were essentially limited to the substantia nigra, where there was extensive loss of neurons in both the zona compacta and the zona reticularis bilaterally. There was some pigment in macrophages, and there was gliosis. No well-marked Luys bodies were seen, but occasional nerve cells showed a saccular clearing of cytoplasm. There were terminal anoxic changes in some large neurons in the globus pallidus and in the hippocampus. Numerous other tissue blocks from the cerebral hemisphere, brain stem, cerebellum, and spinal cord showed no abnormalities other than congestion.

The brain of III-1 (case 2) at autopsy showed an inconsequential hemangioma in the putamen and globus pallidus, as well as neuronal loss and gliosis of the substantia nigra. The brains of III-5 (case 3) and II-2 (case 4) showed no gross abnormalities at autopsy, but unfortunately, no detailed pathological examinations were performed.

**Biochemical Studies of Other Family Members**

Fasting plasma taurine concentrations were determined on subjects III-7 and III-9 (Fig 1) in the T family, as well as on six of the seven children of patients III-1, III-3, and III-5. These individuals presumably each have a 50% chance of developing the neuropsychiatric disease. Plasma taurine values were entirely normal in five of the six individuals examined in generation IV, as well as in subject III-9. Subject III-7 and one person in generation IV (who is clinically well) were each found to have plasma taurine concentrations more than one standard deviation below the normal mean.

III-7, now aged 49 years, has for 12 months been withdrawn and mentally depressed. She complained of undue fatiguability and of difficulty in thinking clearly, and her husband states that she has marked sleep disorders. However, careful examinations (P.J.A.B.) have so far disclosed no neurological abnormalities. At this time, we cannot tell whether this woman is experiencing the earliest symptoms of the familial disease or whether her apathy and depression are due to other causes. It would certainly be reasonable for her to be depressed due to anxiety about developing the disorder. Her fasting plasma taurine levels have dropped gradually from an original 0.055μmol/ml to recent moderately-reduced values of 0.038μmol/ml and 0.042μmol/ml. However, taurine concentrations in two different specimens of her CSF have been perfectly normal.

In view of the possibility that III-7 might be experiencing the early stages of the disorder, her urinary taurine concentrations were measured, and an oral taurine loading test was performed. As a control subject, we chose a healthy young woman who was taking the same oral contraceptive preparation as that taken by III-7, since it has been shown that urinary taurine excretion can be markedly altered in women on a progesterin-estrogen regimen. While on a normal diet, III-7 excreted 90μmol of taurine per 24 hours, and the control subject excreted 32μmol/24 hours. These values are normal for women receiving progesterin-estrogen oral contraceptives. After an oral load of taurine (0.125 mmol/kg body weight), plasma taurine levels rose in III-7 and in the control subject to maximal values at one hour (0.304μmol/ml and 0.271μmol/ml, respectively), and then fell gradually to reach base-line values at six hours after the load. During this six-hour period, III-7 excreted in her urine 30.6% of the taurine load administered, while the control subject excreted 19.3% of the load she had received. The results of the taurine loading tests indicate that III-7 absorbs taurine normally from the gastrointestinal tract and that she does not lose an abnormal amount of taurine in her urine.

**COMMENT**

**Clinical Course and Genetics**

Each of the six affected members of this family became ill between the ages of 45 and 50, and their illnesses proceeded from first symptoms to death in four to six years. The symptoms, especially in the three brothers of generation III where detailed clinical histories are available, are
strikingly similar. These patients experienced mental depression, fatigue, ability and lethargy, sleep disturbances, and weight loss throughout their illnesses. The three brothers seem to have had an unusual impairment of depth perception. In the latter half of the illness, difficulties in speech, swallowing, and breathing appeared in these patients. They also developed certain features of Parkinsonism late in the disease, such as an impassive facial expression, a tendency to hold the trunk stiffly, and tremor. However, none of the patients in generation III developed the full-blown picture of Parkinsonism.

Furthermore, they did not show disordered ocular movements, atrophy, or postural hypotension. Dementia was never prominent and, when present, occurred only late in the disease, whereas depression of mood was an early and prominent symptom. A striking late feature in each of the three brothers in generation III was dyspnea at rest, and each died rather unexpectedly of respiratory failure.

The disorder appears to be inherited as an autosomal dominant (Fig 1), with about half of offspring who reach age 50 developing the illness and with both sexes being affected. This hereditary pattern is similar to that in the reported pedigrees where Parkinsonism has been inherited in an autosomal dominant fashion. However, in most of the pedigrees, symptoms commenced at earlier ages than in our family, the disorder(s) took longer to run their course, and mental depression and lethargy were not clinical features.

**Possible Sources of the Taurine Deficiency**

It is uncertain whether the taurine deficiency we observed terminally in patient III-3 (case 1) was causally related to his symptoms or whether the other affected patients had a similar lack of taurine in blood, CSF, and brain. We also do not know whether equally or more strikingly low taurine levels might have been found in other regions of III-3's brain or in other taurine-containing tissues, such as skeletal and cardiac muscle, had these tissues been examined. Answers to these questions must await biochemical studies of similar patients.

If the taurine deficiency proves to be a key part of the pathogenesis of this genetic disorder, it might arise by one of two mechanisms. Taurine is consumed in man's diet, primarily in mollusks, fish, poultry, and meat, and it is synthesized in at least the liver and the brain from cysteine. Figure 2 shows the relevant pathways of taurine metabolism in man, and those known to occur in human brain are shown by heavy arrows in Fig 2. Cysteine is oxidized to cysteinesulfonic acid, which is then decarboxylated to hypotaurine, the decarboxylase being a pyridoxal phosphate-requiring enzyme. Hypotaurine is then oxidized further to taurine. A small portion of taurine in rat brain is further metabolized to isethionic acid, and isethionic acid presumably also occurs normally in human brain. Further synthetic pathways from cysteine to taurine proceed from cysteamine through hypotaurine and from cysteinesulfenic acid through cysteic acid. The latter pathway is important in birds and may not occur in man.

Since no traces of cysteinesulfinic acid, cysteic acid, or hypotaurine were detectable in the brain samples of patient III-3, it is unlikely that his taurine deficiency could have been due to a block in the synthetic pathways distal to cysteinesulfonic acid. However, an enzymatic block either in the oxidation of cysteine to cysteinesulfenic acid, or in the pathway from coenzyme A through cysteamine to hypotaurine, would not have been detected by our procedures and might have produced the deficiency in brain taurine.

Another possible explanation for III-3's taurine deficiency might have been failure in the absorption of taurine from the lumen of the intestine, or from the glomerular filtrate in the renal tubules, or both. Because the appropriate biochemical studies were never done on the patient's urine, this possibility cannot be ruled out. However, if the patient's sister, III-7, is in the early stages of the same disease, her normal absorption of taurine from the gastrointestinal tract, as well as her normal urinary taurine excretion, would not support this possibility.

The low taurine content of the patient's brain is most unlikely to have been caused by nutritional failure, since he had no other amino acid deficiencies, and since taurine is not decreased in the brains of patients dying with Huntington chorea, where weight loss and potential nutritional failure usually precede death. The patient's taurine deficiency is also unlikely to have been drug-induced. Plasma and CSF taurine levels were normal in other patients receiving amantadine hydrochloride and ethopropazine hydrochloride, the only drugs with which our patient was treated in the weeks before his death.

**Relationship Between Taurine Deficiency and Symptoms**

It may be that the low levels of taurine found in the blood, CSF, and brain of the patient we studied were unrelated to his symptoms. However, it is tempting to speculate that taurine deficiency might have caused some of these symptoms. Although taurine is a major amino acid in muscle and nervous tissue, its physiological role is not well understood. Human brain contains large amounts of taurine, its content being highest in the cerebellar cortex among those regions that have been studied. Taurine inhibits the firing of central neurons in brain, as does GABA, and there is some evidence that taurine may serve as an inhibitory synaptic transmitter or modulator in the central nervous system, as well as in the retina. Hence, a widespread deficiency of taurine might be expected to produce a variety of neurological and psychiatric symptoms and, possibly, even abnormalities in visual perception. Taurine is converted into taurocholic acid, a major bile salt that aids in the intestinal absorption of fat, and it is conceivable that a deficiency in biliary taurocholic acid might have caused the steatorrhea found in patient III-3 and have contributed to the marked weight loss observed in most of the affected members of this family.
Possible Therapy for the Disorder

If biochemical studies of future patients with hereditary depression and parkinsonism should confirm that low levels of taurine in physiological fluids, brain, and other tissues are characteristic of this disorder, it might be possible to treat such patients by giving them taurine. Peck and Awapara27 reported detecting both 35S- and 14C-labelled taurine in rat brain after the corresponding radioactive taurines had been injected intraperitoneally. We have recently found that substantial amounts of 35S-labelled taurine enter brain cells when radioactive taurine is administered orally to the rat or is injected intramuscularly into the squirrel monkey.23

Oraladministration of taurine to normal human subjects is followed by a prompt rise in plasma taurine concentrations, without any obvious untoward effects. Repeated oral doses of taurine, approximately 0.125 mmol/kg every six hours, ought to maintain steadily elevated blood levels of taurine, and these should in turn cause taurine to cross the blood-brain barrier. If the deficiency of taurine in brain in this disorder is the result of failure to synthesize the amino acid, such a therapeutic strategy might prove beneficial. However, since it is possible that taurine only becomes diminished in plasma and CSF late in the course of this disorder, it may be difficult to show the appropriateness of taurine administration.

We suggest that other investigators measure taurine in physiological fluids, and in brain obtained at autopsy, in patients who suffer inherited forms of mental depression, including those with parkinsonism features. Our experience here and recent progress in studies of the pathogenesis of Huntington chorea14,23 emphasize the importance of carrying out biochemical investigations, especially of the brain, in a wider variety of inherited psychiatric and neurologic diseases whose causes are presently unknown.

REFERENCES