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Hartnup Syndrome

By L. I. Woolf, Oxford

In 1956 *Dent* and co-workers described a new syndrome in a boy of 12. He had a red scaly dermatitis affecting head, neck, hands and lower legs, which was worse in summer than in winter. He was mildly ataxic with unsteady gait, tremor, nystagmus and ptosis. The mother stated that an older child had had a similar condition described as pellagra.

True dietary pellagra occurs in maize-eating communities where the diet is deficient in tryptophan and nicotinamide. It is almost unknown in Britain. Familial pellagra is in any case extremely rare.

This child was found to have a high excretion of amino-acids, from 10 to 40 times normal, with a very constant and characteristic chromatographic pattern. He also excreted indole derivatives in large but variable amounts. 3 of his 7 sibs exhibited exactly the same amino-acid pattern and an abnormal indole excretion, the other 4 sibs and the parents never showed any abnormality. Since then 11 other cases in 8 sibships have been described.

Chemistry

The blood amino-acid content is normal or low, hence the amino-aciduria is renal in origin. The pattern of urinary amino-acids is very constant and characteristic, both from case to case and at different times in the same patient. In particular proline is absent (distinction from generalised renal amino-aciduria), and the excretion of cystine, lysine and arginine is normal (contrast cystinuria). This is evidently a defect of renal tubular reabsorption affecting a specific, though large, group of amino-acids.

What of the indole derivatives in the urine? *Milne, Crawford, Girao* and *Loughridge* (1960) have shown that tryptophan is absorbed from the gut much more slowly in Hartnup syndrome than in the normal. It seems probable that tryptophan is acted on by the gut flora to produce abnormal amounts of indole and indole derivatives, which are then absorbed, conjugated and excreted. If neomycin is fed, excretion of indole derivatives becomes normal. There appears to be a general defect

of amino-acid transport, both from the lumen of the gut into the intestinal wall and from the glomerular filtrate into the cells of the proximal renal tubule.

Is there, in addition, a defect of tryptophan metabolism? Normally tryptophan is metabolised first to kynurenine and eventually to nicotinic acid. A block anywhere in this metabolic path would lead to a deficiency of nicotinic acid, and so, probably, to pellagra. In fact *Milne* et al. (1960) showed that, after a test dose of tryptophan, less kynurenine is excreted in Hartnup syndrome than in the normal. This suggests a deficiency of tryptophan pyrrolase, but it may only reflect a transport defect into the cells.

Clinical Aspects

The clinical features are very variable, both from patient to patient and in the same patient from time to time. Dermatitis, worse in the summer months and on exposed areas, frequently occurs. Attacks of cerebellar ataxia are common, but some patients escape. Some patients have psychological disturbances ranging from emotional instability to delirium with hallucinations. There is little or no evidence of intellectual defect. In one case severe headache was the only symptom or sign of involvement of the central nervous system.

Patients tend to improve as they get older, with fewer ataxic episodes, improved behaviour, and less susceptibility to dermatitis. Large regular doses of nicotinamide are said to be helpful.

Relation of biochemistry to clinical signs

There is almost certainly a lack of nicotinic acid. This is due partly to the diversion of tryptophan to other paths–indican etc.–and partly to a failure to metabolise tryptophan normally. In dietary pellagra it has repeatedly been suggested that maize contains toxic indole derivatives that, together with the lack of nicotinic acid and tryptophan, cause the changes in the skin and nervous system. It is possible that similar toxic substances produced in the gut in Hartnup syndrome are responsible for the intermittent clinical signs. If this is so, it would be rational to sterilise the gut with neomycin during an attack, as well as feeding nicotinamide.

Genetics

There is consanguinity of the parents in three of the eight families with Hartnup disease. This is strong evidence that the condition is due to a recessive gene, and also suggests that the gene is a very rare one.

Summary

Hartnup syndrome is a rare familial disease characterised by a variable photo-sensitive dermatitis and intermittent attacks of cerebellar ataxia. There may also be mental disturbances. It closely resembles pellagra. Children are worse affected than adults. There is a constant excretion of amino acids and an intermittent excretion of indole derivatives in the urine. Because of a recessively inherited defect in amino acid transport, amino acids are only slowly and inefficiently (1) absorbed from the gut and (2) re-absorbed in the proximal renal tubule from the glomerular filtrate. As a result of (1), amino acids derived from the diet undergo bacterial attack in the colon causing excessive production of indole derivatives from tryptophan. (2) causes the characteristic aminoaciduria. The loss of tryptophan in the urine and by bacterial attack in the gut reduces the production of nicotinic acid; this is further reduced by diminished conversion of tryptophan to kynurenine in the body in Hartnup disease. Giving nicotinamide helps these patients; giving neomycin by mouth during an attack may also be helpful.

Zusammenfassung

Das Hartnup-Syndrom ist eine seltene familiäre Erkrankung, die charakterisiert ist durch eine wechselnde, lichtempfindliche Dermatitis und intermittierende Anfälle von cerebellärer Ataxie. Auch geistige Störungen können auftreten. Das Syndrom gleicht dem Bild der Pellagra sehr. Kinder sind stärker betroffen als Erwachsene. Es besteht eine dauernde Ausscheidung von Aminosäuren und eine intermittierende Ausscheidung von Indolderivaten im Urin. Wegen eines rezessiv vererbbaren Ausfalls im Aminosäurentransport werden die Aminosäuren vom Darm nur langsam und wenig wirkungsvoll aufgenommen (1) und im proximalen Nierentubulus aus dem Glomerulusfiltrat rückresorbiert (2). Als Ergebnis von (1) unterliegen Aminosäuren, die von der Nahrung herkommen, einem bakteriellen Abbau im Colon, der eine stark vermehrte Bildung von Indolderivaten aus dem Tryptophan bewirkt. (2) verursacht die kennzeichnende Aminoacidurie. Der Verlust von Tryptophan im Urin und der bakterielle Abbau im Darm vermindern die Produktion der Nikotinsäuren, eine Verminderung, welche durch die bei der Hartnupkrankheit im Körper verringerte Umwandlung von Tryptophan in Kynurenin noch verstärkt wird. Gaben von Nikotinsäureamid helfen diesen Patienten. Orale Gaben von Neomycin während eines Anfalls können ebenso nützlich sein.

Résumé

Le syndrôme de Hartnup est une affection familiale rare, qui est caractérisée par une dermatite photosensible variable et par des atteintes intermittentes d'ataxie cérébelleuse. On rencontre aussi quelquefois des troubles mentaux. Cette affection ressemble beaucoup à la pellagre. Les enfants ont des atteintes plus fréquentes et plus fortes que les adultes. On trouve dans l'urine une excrétion constante d'acides aminés et une excrétion intermittente de dérivés indoliques. A cause d'un défaut héréditaire récessif dans le transport des acides aminés, l'absorption intestinale est trop lente (1) et la réabsorption par les parties proximales des tubuli rénaux à partir du filtrat glomérulaire est inefficace (2). A la suite de (1), les acides aminés provenant de la nourriture sont soumis au gros intestin à une décomposition bactérienne et il en résulte une production exagérée de dérivés indoliques à partir du tryptophane, (2) cause l'amino-acidurie caractéristique. La perte de tryptophane dans l'urine et l'action bactérienne dans l'intestin diminuent la production d'acide nicotinique; cette diminution est encore accentuée dans la maladie de Hartnup par une diminution de la transformation du tryptophane en kynurénine dans l'organisme. L'administration de nicotinamide peut améliorer l'état de ces malades; l'administration de néomycine par voie buccale au cours d'une attaque serait également utile.

Riassunto

La sindrome di Hartnup è una rara malattia famigliare caratterizzata da una dermatite foto-sensibile variabile ed attacchi intercorrenti di atassia cerebellare. Possono anche esistere disturbi psichici. La malattia somiglia strettamente alla pellagra. I bambini ne sono più gravemente affetti che gli adulti. L'urina contiene costantemente amino-acidi e ad intermittenza derivati d'indolo. In seguito ad un difetto ereditario recessivo del trasporto degli aminoacidi si ha un lento ed insufficiente (1)assorbimento intestinale e (2) riassorbimento dal filtrato glomerulare nel tubulo renale prossimale. In seguito ad (1) gli amino-acidi della dieta subiscono l'attacco dei batteri del colon dando origine ad una produzione eccessiva di derivati indolici del triptofano. (2) causa il caratteristico reperto dell'amino-aciduria. La perdita di triptofano nell'urina e in seguito l'azione batterica nell'intestino diminuiscono la produzione di acido nicotinico; questo acido è inoltre diminuito in seguito alla ridotta trasformazione di triptofano in kynurenina, che si constata nella malattia di Hartnup. La somministrazione di amide dell'acido nicotinico giova a

questi pazienti; la somministrazione orale di neomicina durante l'attacco può pure giovare.

Baron D. N., Dent C. E., Harris H., Hart E. W. and *Jepson J. B.:* Hereditary pellagra-like skin rash with temporary cerebellar ataxia, constant renal amino-aciduria and other bizarre biochemical features. Lancet **1956**/II, 421.

Henderson W.: A case of Hartnup disease. Arch. Dis. Childh. **33,** 114 (1958).

Hersov L. A. and *Rodnight R.:* Hartnup disease in psychiatric practice: clinical and biochemical features of three cases. J. Neurol., Neurosurg. Psychiat. **23,** 40 (1960).

Jepson J. B. and *Spiro M. J.:* Hartnup Disease, in: *Stanbury J. B., Wyngaarden J. B.* and *Fredrickson D. S.:* The Metabolic Basis of Inherited Disease, p. 1338. McGraw-Hill, New York 1960.

Jonxis J. H.: Oligophrenia phenylpyruvica en de Hartnupziekte. Ned. T. Geneesk **101,** 569 (1957).

Milne M. D., Crawford M. A., Girao C. B. and *Loughridge L. W.:* The metabolic disorder in Hartnup disease. Quart. J. Med. **29,** 407 (1960).

Shaw K. N. F., Redlich D., Wright S. W. and *Jepson J. B.:* Dependence of urinary indole excretion in Hartnup disease upon gut flora. Fed. Proc. **194** (1960).

Weyers H. and *Bickel H.:* Photodermatose mit Aminoacidurie, Indolaceturie, und cerebralen Manifestationen (Hartnup-Syndrom). Klin. Wschr. **36,** 893 (1958).

Halvarsen K. and *Halvarsen S.:* to be published.