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Menstrual Cycle and Gonadal Steroid Effects on Symptomatic Hyperammonaemia of Urea-cycle-based and Idiopathic Aetiologies

W. W. GRODY[1,2,6]*, R. J. CHANG[3]†, N. M. PANAGIOTIS[4,7], D. MATZ[8] and S. D. CEDERBAUM[1,5,6]

[1]*Division of Medical Genetics, Departments of* [2]*Pathology and Laboratory Medicine,* [3]*Obstetrics and Gynecology,* [4]*Medicine,* [5]*Psychiatry, and* [6]*Pediatrics;* [6]*Mental Retardation Research Center, UCLA School of Medicine, Los Angeles, CA 90024-1732; Departments of* [7]*Medicine and* [8]*Obstetrics and Gynecology, Northridge Hospital Medical Center, Northridge, CA, USA*

Summary: We report two female patients, one with a known inborn error of ureagenesis and the other of unknown cause, in whom recurrent, transient episodes of severe hyperammonaemia increased in frequency and severity with sexual maturity and parturition. Both responded to ovarian steroids administered continuously to suppress ovulation and menstruation, and ultimately to simple hysterectomy. These studies suggest a new therapeutic approach to defective ureagenesis in female patients and a relationship between ammonia production or disposal and the menstrual cycle.

Elevated plasma ammonia, with its attendant encephalopathic effects, is seen in a diverse group of disorders in infants, children and adults, including hereditary deficiency of any of the five enzymes of the urea cycle (Brusilow and Horwich 1989), end-stage liver disease (Hoyumpta et al 1979), Reye syndrome (Shannon et al 1975), transient hyperammonaemia of the newborn (Hudak et al 1985), the hyperornithinaemia–hyperammonaemia–homocitrullinuria (HHH) syndrome (Shih et al 1969), lysinuric protein intolerance (Carson and Redmond 1977), and as a secondary phenomenon in the organic acidaemias (Nyhan and Sakati 1987), systemic carnitine deficiency (Chapoy et al 1980), urinary tract infection (Santoy and DeBenkelaer 1980), ureterosigmoidostomy (Guillaume et al 1988), administration of valproate (Hjelm et al 1986) and asparaginase (Moure et al 1970), and chemotherapy of haematological malignancies (Watson et al 1985). Clinical signs of hyperammonaemia include cerebral oedema with altered mental status, electroencephalographic changes, vomiting, seizures, and coma that can be fatal (Catherlineau 1979). The episodic hyperammonaemia that occurs in inborn errors of metabolism is thought to be due, in large part,

*Correspondence

†Current address: Department of Obstetrics and Gynecology, University of California, Davis
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to endogenous catabolism occurring in response to fever or infection or the need for glucogenesis in anorexia and poor caloric intake (Brusilow and Horwich 1989). The frequency and severity of these episodes often diminish as the patients grow and mature. More recently acute hyperammonaemia has been described in carriers of ornithine transcarbamylase deficiency, for the first time in association with the catabolism occurring at the time of labour and delivery (Arn et al 1990). Modern treatments encompass dietary protein restriction to reduce the exogenous nitrogen load (Brusilow and Horwich 1989), lactulose and neomycin to suppress ammonia formation by intestinal bacteria (Flannery et al 1982), haemodialysis or peritoneal dialysis (Batshaw and Brusilow 1980), arginine and citrulline supplementation to drive the substrate-depleted urea cycle in children with inborn errors (Brusilow and Batshaw 1979), and administration of sodium benzoate and/or sodium phenylacetate to promote urinary excretion of waste nitrogen as hippurate and phenylacetylglutamine, respectively (Batshaw et al 1982). Some combination of these regimens is usually sufficient to lower plasma ammonia levels during both acute hyperammonaemic crisis and chronic maintenance therapy, and can be more effective if begun promptly in the face of an imminent rise of blood ammonia.

It is obviously relevant then to identify patients and less well-known situations placing these patients at risk for developing hyperammonaemia. We report two female patients, one with a known inborn error of ureagenesis, arginase deficiency, and the other of idiopathic aetiology, in whom recurrent, transient episodes of severe hyperammonaemia increased in frequency with sexual maturity and parturition, both of whom responded dramatically first to ovarian steroids used to completely suppress ovulation and menstruation, and ultimately to a simple hysterectomy. These studies highlight a novel therapeutic approach to defective ureagenesis in female patients and suggest a physiological connection between ammonia production or disposal and the menstrual cycle.

PATIENTS AND METHODS

Patient 1: Patient R.U. is a 28-year-old woman with liver arginase deficiency (McKusick 207800) diagnosed by red blood cell assay (Spector et al 1980) at age 12 years (arginase activity $< 10\,\mu$mol urea/h per g protein; control = 1000; Cederbaum et al 1979). The diagnosis has since been confirmed at the molecular level by demonstration that she is homozygous for a nonsense mutation in exon 4 of the liver arginase gene (Vockley et al 1994). She is severely retarded (IQ 15) and suffers from small stature and spasticity but, as is typical for and unique to this urea cycle defect (Cederbaum et al 1979), was spared significant hyperammonaemic crises in infancy and childhood. With menarche at age 18 years, well after the initiation of specific dietary therapy, a cyclical pattern of transient but severe hyperammonaemia (values up to $222\,\mu$mol/L) leading to coma ensued. It eventually became apparent that these episodes were remarkably and consistently coincident with the menstrual periods, with lapse into coma beginning on the first day of menstruation and spontaneous recovery commencing three days later. This phenomenon occurred during each menstrual period over the course of $1\frac{1}{2}$ years, despite appropriate maintenance

therapy consisting of dietary protein restriction and sodium benzoate. Elevated ammonia levels were documented during most of these episodes. A pelvic examination and pelvic ultrasound were normal. The patient had a 22-year-old brother (now deceased) who also had arginase deficiency with mental retardation; he never showed increased frequency of hyperammonemic episodes with sexual maturity, although his responses to therapy were otherwise similar.

Patient 2: Patient I.D. is a 33-year-old woman who reported a vague history of episodic altered mental status and allergic reactions in childhood and young adulthood but was generally in good health until 4 months into her only pregnancy, at age 27 years, when she experienced apparent psychomotor seizures. At the time of delivery by Caesarean section, she lapsed into a coma shortly after awakening from anaesthesia. Plasma ammonia levels drawn at this time reached as high as 500 μmol/L. The patient was treated with intravenous sodium benzoate, arginine and intravenous alimentation but still required 2 weeks to emerge from coma. She then spent almost the entire following year in the hospital with waxing and waning elevation of ammonia levels. Her symptoms included nausea and vomiting, severe headache, clouded mental status and slurred speech, though she never again became comatose. The episodes occurred at the rate of 2–3 per week, with peak ammonia levels documented between 138 and 4781 μmol/L. The patient refused sodium benzoate, whether intravenously or by mouth, claiming that it caused vomiting, abdominal cramps and burning at the infusion site. Therefore, treatment of these episodes was largely supportive, consisting of intravenous fluids, antiemetics and analgesics, with the typical pattern being resolution in 2–3 days without obvious correlation with specific exogenous manipulations. A low-protein diet was instituted, but this, too, could not be correlated with any clinical response. The possibility of Munchausen syndrome was raised on more than one occasion, but could never be documented and would not have accounted for the coma at time of Caesarian section in any case. The patient had had a tubal ligation following delivery and was using no contraceptives but, unlike patient R.U., there was no obvious chronological relation between the hyperammonaemic episodes and regular menstrual cyclicity. Aside from the ammonia, all other liver function tests, including bilirubin, serum transaminases and two histological biopsies, have consistently been normal. Plasma amino acid analyses showed variable minor deviations from normal that were not diagnostic of any particular disorder.

Biochemical assays: All procedures conformed to the guidelines of the Human Subject Protection Committee of UCLA Medical Center. Red blood cell arginase assays were performed by a modification of the [^{14}C]uridoarginine cleavage reaction of Schimke (1964), as previously decscribed (Spector et al 1980). The allopurinol challenge test for carriers of ornithine transcarbamylase deficiency was conducted as outlined by Hauser et al (1990) and the urine orotic acid levels were assayed in their laboratory. Assay of liver tissue for activity of carbamylphosphate synthetase and ornithine transcarbamylase was done in Dr Phillip Snodgrass's laboratory according to their published procedures (Kang et al 1973). Plasma ammonia levels were

determined in the UCLA Clinical Laboratories on a DuPont ACA automated analyser. Plasma amino acids were assayed at Children's Hospital of Los Angeles by standard methods (Hammond and Savory 1976). Sodium benzoate and sodium phenylbutyrate were kindly supplied by Dr Saul Brusilow. Dry powdered preparations of L-arginine and L-citrulline were obtained from Ajinomoto Co., Tokyo, Japan.

RESULTS

Patient 1: Although the association of the symptoms and laboratory abnormalities with the menstrual cycle was finally appreciated in R.U., there was no precedent known in gynaecological endocrine physiology to determine whether the impact was hormonal or associated with the physical engorgement, resorption and sloughing of the endometrium. Therefore we began empirical treatment. Cycling with either Ovral® or Lo/Ovral® did not diminish the monthly episodes of hyperammonaemia. The episodes were halted only through suppression of ovulation and bleeding by the continuous administration of Ovral, and recurred only during breakthrough bleeding. High-dose oestrogen and progesterone, administered separately for one month each, suppressed both ovulation and episodic hyperammonaemia.

After one year of successful treatment with this regimen, R.U. was admitted to the hospital for withdrawal of endocrine support and observation. Ammonia, which had regularly been $< 22\,\mu$mol/L, rose to more than $222\,\mu$mol/L on day 11, at which time minimal menstrual spotting was observed. Plasma glutamine rose from normal or slightly above to at least 1.5 times the upper limit of normal.

Recently, after 8 years of successful therapy, the patient underwent total abdominal hysterectomy following the experience of patient 2 (see below). At surgery a normal nulliparous uterus without evidence of leiomyomata or endometriosis was found. She has had no recurrence of hyperammonaemia in $3^1/_2$ years since surgery.

Patient 2: I.D. was admitted to the UCLA Clinical Research Center for a number of special diagnostic studies and therapeutic trials. Citrulline with or without arginine administration (intravenous (IV) or by mouth (PO)) was tried for empirical diagnosis/treatment of lysinuric protein intolerance (Rajantie et al 1980), but this had no effect on ammonia levels. An allopurinol challenge test to rule out heterozygosity for ornithine transcarbamylase deficiency (Hauser et al 1990) was negative. A needle liver biopsy showed essentially normal histology and full activity of carbamylphosphate synthetase and ornithine transcarbamylase (1.01 U and 32.4 U/mg protein, respectively; control values = 1.63 ± 0.42 U and 34.6 ± 0.33 U/mg protein, respectively); deficiency of the other three enzymes of the urea cycle (argininosuccinate synthetase, argininosuccinate lyase, and arginase) was ruled out by the essentially normal plasma amino acid studies. Trials of sodium benzoate and sodium phenylbutyrate, both IV and PO, were initiated but had to be discontinued owing to non-compliance in the face of perceived unpleasant side-effects. The diet was adjusted to various degrees of protein restriction, also without effect.

Throughout this 3-week evaluation, plasma ammonia levels were monitored at regular and frequent intervals around the clock. These revealed a remarkable, almost

daily, fluctuation, though one without obvious circadian rhythm except for the fact that they tended to peak to the most extreme levels (up to 471 μmol/L) late at night. During and prior to several of these rises, the patient was monitored continuously by one of the investigators (W.W.G.) who observed no evidence of self-administration of ammonia or other nitrogenous compounds. Intermittent as well as continuous arginine infusion had no consistently demonstrable effect on this process and were ultimately discontinued for fear that the arginine itself may have been making matters worse by contributing to the nitrogen load.

Thus, at the end of this investigation, patient I.D.'s clinical diagnosis remained one of idiopathic hyperammonaemia not secondary to any known inborn error of metabolism (acetylglutamate synthetase was not studied) nor to any of the other known hepatic, infectious or drug-induced causes of elevated blood ammonia. As a last resort, mindful of our earlier experience with patient R.U., we discharged I.D. with a prescription for suppressive hormonal therapy (Lo/Ovral 1 tablet four times daily continuously). (Her prior menstrual history had always been entirely normal, with regular periods and no menorrhagia.)

During the first month of this regimen, she was readmitted several times to her local community hospital with the familiar symptomatology of transient hyperammonaemia. By the second month, however, these episodes dwindled, and for the subsequent 11 months on continuous oral contraceptive therapy and an *ad libitum* diet she remained completely asymptomatic and virtually normoammonaemic, her only hospital admission during this period being for removal of a lipoma (which she tolerated without incident). At this point we opted for a trial off hormonal therapy. The patient experienced some irregular withdrawal bleeding but otherwise did well for the next 3 months. Then her familiar symptoms recurred and she was admitted to the hospital with ammonia values reaching 194 μmol/L. She was placed back on Lo/Ovral, with rapid relief of symptoms and return of blood ammonia levels to the normal range. Unfortunately, heavy breakthrough bleeding at this time necessitated another unplanned discontinuation of the Lo/Ovral. Ammonia levels again rose into the 194 μmol/L range with recurrence of severe headache and delirium. Hormones were again resumed, and within two days the ammonia had dropped into the extreme low-normal range (values as low as 6 μmol/L) with lasting relief of symptoms.

Following a successful year of therapy (punctuated by one hospitalization for hyperammonaemia resulting from breakthrough bleeding), the patient elected what was hoped might be a permanent solution to her problem. After obtaining full informed consent, a total abdominal hysterectomy was performed. Neither leiomyomata nor endometriosis was found at the time of surgery. In the 4 years since surgery, with no hormonal intervention, no hyperammonaemia or symptoms related to it have occurred.

DISCUSSION

These studies in two female patients with recurrent episodes of severe hyperammonaemia suggest a previously unsuspected relationship between ureagenesis and the menstrual cycle. One of these patients (R.U.) has a known inborn error of the urea cycle (arginase deficiency); the other (I.D.) expresses a defect at some unknown locus,

presumably in an enzymatic pathway that impinges in some manner on the urea cycle. In both patients the occurrence of hyperammonaemia and coma was tied circumstantially to endogenous sex steroid levels of the female menstrual cycle: in R.U. the crises began at menarche and coincided precisely with the menstrual periods; in I.D. the episodes began after childbirth and were more or less continuous from then on. Both patients attained complete relief upon suppression of the pituitary–ovarian axis by administration of suppressive noncyclic doses of an exogenous oestrogen–progesterone mixture and now by hysterectomy alone.

At the time these observations were made there was no precedent for them. More recently, however, Arn and colleagues (1990) have reported a cohort of heterozygotes for ornithine carbamoyltransferase deficiency (a gene defect located on the X-chromosome) in whom the first episode of hyperammonaemia coincided with parturition and in whom subsequent episodes occurred in conjunction with the menstrual cycle.

The explanation for this curious phenomenon can only be speculated upon at present. One possibility is that the cyclic sex steroid-induced hyperplasia, resorption and sloughing of endometrium and blood produces excessive nitrogenous waste that cannot be adequately handled by the urea cycles of these patients, which are already operating at borderline efficiency owing to genetic inborn errors of metabolism. (It should be noted that patient R.U. has the one type of urea-cycle defect – liver arginase deficiency – in which there is persistent, low-level ureagenesis supplied by a second form of arginase (isozyme AII) located primarily in the kidney (Grody et al 1989).) The addition of bacterial action on these sloughed uterine products could render the situation analogous to that of the end-stage cirrhotic patient whose gastrointestinal bleeding contributes to the encephalopathy. If this theory is true, then the ultimate curative therapy would be hysterectomy, a course we have demonstrated to be effective in these two patients.

Another possibility is that the endogenous sex steroids themselves are directly perturbing the regulation or function of the urea cycle or some ancillary pathways feeding into it. Adrenocortical steroids are known to induce the expression of genes for some of the urea-cycle enzymes *in vitro* (Haggerty et al 1982; Morris et al 1987); conceivably, gonadal steroids might have a contrary effect. Our ability to maintain normoammonaemia with continuous ovulatory suppression by high-dose oestrogen, progesterone or a balanced oral contraceptive reduces the probability of such a scenario, but does not eliminate it entirely. The success of hysterectomy alone in controlling hyperammonaemia is, however, virtual proof of the primary role of uterine cycling in this process, despite the lack of an obvious temporal connection with menses in patient I.D. If the hormone theory is true, then both of our patients will ultimately require bilateral oophorectomy, an eventuality that seems unlikely in view of their follow-up courses so far. In any case, the mechanism is likely to be rather complex, since in patient R.U. the hyperammonaemia appeared to coincide with resolution of oestrogen and progesterone secretion associated with the onset of menses and endometrial sloughing in the menstrual cycle, while in patient I.D. the hyperammonaemia began after the drastic fall of oestrogen and progesterone and the catabolism and tissue resorption brought on by parturition, with no apparent prior or subsequent relationship to menses.

The phenomenon of exacerbation of hyperammonaemic episodes in older patients with urea-cycle defects is not unknown. A cohort of Japanese patients, both females and males, with citrullinaemia due to argininosuccinate synthetase deficiency regularly had their first episodes of obvious hyperammonaemia in their late teens or twenties, despite the fact that the disorder may already have resulted in mental retardation in some of them (Yajima et al 1981; Matsuda et al 1982). We have recently reported sudden onset of fatal hyperammonaemia in two adult patients with arginase deficiency (Grody et al 1993). These reports suggest the occurrence of some circadian protein catabolic episodes in all adults, without so obvious a marker as the menstrual period, and to which other disorders of amino acid or organic acid metabolism may also be theoretically vulnerable.

In any event, our studies do point to a hitherto unrecognized connection between ureagenesis and the menstrual cycle, and suggest the utility of a trial of suppressive oral contraceptive therapy in any post-pubertal female patient with recurrent or transient hyperammonaemia that is refractory to other approaches.

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J. Inher. Metab. Dis. 17 (1994) 574

BOOK REVIEW

New Horizons in Neonatal Screening. Edited by J.-P. Farriaux and J.-L. Dhondt. International Congress series 1041, Excerpta Medica, Amsterdam and New York, 1994. ISBN 0-444-81602-X, 408pp, Dfl.325/$185.75.

This book covers the proceedings of the 9th International Screening Symposium and the 2nd Meeting of the International Society for Neonatal Screening, held in Lille, France, in September 1993. Although the title might suggest a rather dry catalogue of reports on neonatal screening programmes around the world, the volume contains much more besides. Important questions of ethical and legal issues are addressed. Screening for treatable conditions such as PKU, where fully informed consent can be given, is one thing but with the recent advances in DNA technology our innermost secrets are now open to scrutiny by unscrupulous molecular biologists. Responsibility for blood spots and strict maintenance of confidentiality are rightly discussed.

Other sections deal with neonatal screening, prenatal screening and technical aspects as well as quality control. The major section on neonatal screening covers well established and cost-effective programmes through to screening for MELAS and MERRF. Goodness knows how one would counsel a family where the MELAS mutation is found in a newborn. Other conditions that are discussed include hyperphenylalaninaemia, hypothyroidism, congenital adrenal hyperplasia, galactosaemia, haemoglobinopathies, cystic fibrosis, neuroblastoma, hyperlipoproteinaemia and fatty acid oxidation defects. Prenatal screening takes us from triple screening for Down syndrome to chromosome analysis in fetal cells derived from maternal blood, as well as prenatal diagnosis of organic acid disorders by GC–MS analysis of amniotic fluid. The final section deals with some high-tech aspects such as screening for metabolic disorders by tandem MS and automated screening of molecular genetic defects using blood spots. This nicely takes us back to the beginning and the versatility of the dried blood spot. The concluding remarks extol the virtues of filter paper technology and the potential for all manner of tests, not just in newborns, and the value particularly for underdeveloped countries.

Although something of a pot-pourri, this book contains something to satisfy all tastes, particularly those involved with all aspects of screening as well as metabolic disease.

G. T. N. Besley