Suid-Afrikaanse Tydskrif vir Geneeskunde

South African Medical Journal

VAN DIE REDAKSIE

ONLANGSE VORDERING INSAKE OORMATIGE BYSKILDKLIERWERKING

Dit word vandag algemeen aangeneem dat slegs die minderheid van pasiënte met oormatige byskildklierwerking aan die beensiekte wat korrek bekend staan as verspreide osteitis fibrosa ly. Die meeste pasiënte presenteer klinies met niersteine, en kom dus vroeg onder die behandeling van die uroloog. Dit is welbekend dat die stene kalsiumoksalaat en fosfaat bevat, dat hulle ondeurstraalbaar is, dat hulle dikwels groot is en vertakkings het, en dat daar 'n sterk neiging tot newebesmetting is. Slegs 'n klein persentasie van sulke stene staan werklik in verband met oormatige byskildklierwerking, maar dit is baie belangrik om dit in laasgenoemde gevalle uit te ken, omdat snykundige ingreep gewoonlik die enigste hoop aanbied om die pasiënt van die dood weens nierversaking te red. Die volgende prosedure moet gevolg word wanneer 'n kalsium-bevattende niersteen ontdek word. 'n Vroegoggend- (of 24-uurlikse) urinemonster word vir kalsium getoets volgens die eenvoudige metode waarby die Sulkowitch-reagens gebruik word. Indien hierdie toets 'n groot hoeveelheid kalsium aandui, moet 'n serummonster getoets word vir sy gehalte aan kalsium, anorganiese fosfor en alkaliese fosfatase. 'n Verhoogde serum-kalsiumgehalte en verminderde fosfor-inhoud kan beskou word as kenmerkend van oormatige byskildklierwerking—mits die berekening natuurlik volkome betroubaar is. Indien die inhoud aan alkaliese fosfatase vermeerder is, moet die skelet en tande met X-strale ondersoek word om vas te stel of daar tekens is dat die beenresorpsie van osteitis fibrosa plaasvind.

Die moeilikheid onstaan waar die uitslae nie heeltemal duidelik is nie. As die urine-inhoud aan kalsium hoog bly (meer as 200 mgm. per 24 uur op 'n gewone dieet) moet die serum-ontleding, indien dit aan die begin normaal was, verskeie male herhaal word voordat oormatige byskildklierwerking uitgesluit kan word; die diagnose van ‚idiopatiese hiperkalsiurie' word dan gemaak. In die verbygaan kan daarop gelet word dat die ietwat ongemaklike kalsiumarm-dieet tans nie meer as nodig of behulpsaam by uitkenning beskou word nie—'n urine-kalsium van meer as 200 mgm. daagliks op 'n normale dieet moet as verdag bereken word. Die volgende moeilikheid ontstaan by dié gevalle waar die beensiekte nie voorkom nie en die serum-kalsium-gehalte verhoog is (dikwels net by tye) maar waar die serum-fosfor binne normale perke bly. 'n Kombinasie van hierdie aard kan by verskeie ander siektes aangetref word, o.a. sarkoïedose, karsinomatose, miëlomatose, beriellose, en die Cushing-sindroom. Hierdie siektes kan gewoonlik maklik uitgeskakel word—mits hulle darem oorweeg word.

EDITORIAL

RECENT ADVANCES CONCERNING HYPERPARATHYROIDISM

It is now widely appreciated that only the minority of patients with hyperparathyroidism suffer from the bone disorder, which is correctly known as generalised osteitis fibrosa. The great majority present with renal calculi, and consequently fall early into the hands of the urologist. As is well known, the calculi contain calcium oxalate and phosphate, are radio-opaque, frequently large and branched, and very liable to secondary infection. Only a small proportion of such calculi are actually associated with hyperparathyroidism, but the recognition of the latter where it exists is extremely important, since its surgical correction is usually the only chance of saving the patient from eventual death from renal failure. The procedure which should be adopted on discovery of a calcium-containing calculus is as follows. An early morning (or 24 hour) specimen of urine is tested for calcium by the simple method using Sulkowitch's reagent. If this test indicates a large quantity of calcium, a sample of serum is then analysed for calcium, inorganic phosphorus, and alkaline phosphatase content. A raised serum calcium and lowered phosphorus may then be considered diagnostic of hyperparathyroidism, provided, of course, that the estimation is completely reliable. If the alkaline phosphates is raised, the skeleton and the teeth should be X-Rayed for evidence of the bone resorption of osteitis fibrosa.

Difficulty arises where the results are less clearcut. When the urine calcium remains high (over 200 mgm. per 24 hours on a normal diet) the serum examinations if at first normal, must be repeated several times before hyperparathyroidism can be excluded, in which case the diagnosis becomes 'idiopathic hypercalciuria'. It may be noted in passing that the rather awkward 'low calcium diet' is no longer thought to be necessary or helpful in the diagnosis—a urine calcium over 200 mgm. per day on normal diet must be considered suspicious. The next difficulty is in those cases without bone disease, in which the serum calcium is elevated (often only intermittently) but the serum phosphorus remains within normal limits. A combination of this sort may be found in various other conditions, including sarcoidosis, carcinomatosis, myelomatosis, beryllosis and Cushing's syndrome.

Soms is sarkoïedose egter baie moeilik en 'n terapeutiese proef-behandeling met kortisoon (wat die oormaat bloed-kalsium van sarkoïed sal verminder, dog nie dié van oormatige byskildklierwerking nie) sal moontlik 'n nuttige toets wees.

Daar sou geen moeilikheid wees nie indien die serum-fosfor sonder uitsondering van lae konsentrasie was by oormatige byskildklierwerking nie, omdat osteomalakie die enigste ander siekte is waarby hierdie verskynsel voorkom.

Dit kom tog soms voor dat die serum-fosforgehalte binne die normale perke bly, en dit is moontlik selfs verhoog as daar nierversaking was. Laasgenoemde verwikkeling lewer ook sekere moeilikhede op, aangesien die nierversaking self (waarskynlik omdat dit die verlies van liggaamskalsium veroorsaak) sekondêre oormatige byskildklierwerking en beenvernietiging veroorsaak. Dit is dus moontlik, en wel gerapporteer, dat 'n pasiënt terselfdertyd of agtereenvolgend aan beide primêre en sekondêre oormatige byskildklierwerking kan ly.[1] Wanneer nierversaking deur 'n primêre nierkwaal veroorsaak word, is die serum-kalsium nooit vermeerder nie.

Is daar enige ander toetse wat 'n moeilike diagnose kan beklink? Reifenstein en sy medewerkers[2] oorweeg drie nuwe toetse. Die eenvoudigste van die drie is die fosfaat-ontberingtoets. Dit is reeds lankal bekend dat 'n groot fosfor-inname die biochemiese afwykings van oormatige byskildklierwerking grootliks kan uitskakel, en hieruit word dit afgelei dat 'n lae fosfaat-inname hierdie afwykings kan beklemtoon. Hierdie spesiale fosfor-arm-dieet word 3-6 dae lank volgehou (dit is logies om die fosfor-absorpsie verder te verminder deur die gebruik van aluminiumhidroksied), en ná die 3-6 dae is dit heel moontlik dat die serum-fosfor by die hiperparatiroïed-pasiënt na die normale gehalte daal, terwyl daar maar min verandering in die urine-fosfor voorkom. By die normale pasiënt sal dit bevind word dat die serum-fosforgehalte maar min verander het, maar die urine-uitskeiding (van fosfor) behoort sterk te daal.

Die tweede toets is, teoreties altans, fundamenteel. Dit berus op die stelling dat dit een van die grondige aksies van die byskildklierhormoon is om die vermoë van die nierbuisies om fosfor te herabsorbeer te verminder—en dus, mits daar geen ander faktore op die spel kom nie, word die urine-uitskeiding van fosfor vermeerder. Die toets meet dus die werklike kapasiteit van die buisies om fosfor te herabsorbeer. Om dit moontlik te maak, word die serumgehalte aan fosfor verhoog deur aar-inspuiting van bufferfosfaat, en die presiese fosfaat-uitskeiding word dan gemeet. Hierdie berekening word dan in verband gebring met die uitskeiding van kreatinien (of, meer akkuraat, die filtreerspoed van die nierliggaampies word volgens insulien-uitskeiding gemeet). Die fosfaat-uitskeiding is hoër as die normale by oormatige byskildklierwerking (omdat die buisies se heropname onder-normaal is).

Die derde toets is die berekening van kalsium-infusie. By hierdie toets word die serum-kalsium kunsmatig verhoog deur die aar-infusie van kalsiumglukonaat (of 'n soortgelyke saggaraat). Om die een of die ander tans onbekende rede, veroorsaak hierdie metode gewoonlik 'n vermeerdering van ten minste 2 mgm. per 100 ml. in die serum-fosfor by 'n normale mens. By oormatige byskildklierwerking veroorsaak dit 'n baie kleiner styging.

Ons het nog nie baie ondervinding opgedoen insake

These conditions are usually easily excluded, provided they are considered, but sometimes sarcoidosis may be very difficult, and a therapeutic trial of cortisone (which will reduce the hypercalcaemia of sarcoid but not of hyperparathyroidism) may be a useful test.

If the serum phosphorus were always low in hyperparathyroidism it would be easy, because in nothing else except osteomalacia is this phenomenon seen. However, it is not infrequently within the normal range, and may even be elevated if renal failure has occurred. The latter state also brings certain difficulties, since renal failure itself may invoke (probably by causing loss of body calcium) secondary hyperparathyroidism and bone osteoclasis. It is thus possible, and has been recorded, for a patient to suffer both primary and secondary hyperparathyroidism either contemporaneously or consecutively.[1] Where renal failure is caused by a primary kidney condition, the serum calcium is never raised.

Where the diagnosis is difficult, can we look to further tests? Three recent ones are considered by Reifenstein and co-workers.[2] The simplest of these is the phosphate deprivation test. It has long been known that a *high* phosphorus intake may largely abolish the biochemical abnormalities of hyperparathyroidism, so it was conjectured that a low phosphate intake might accentuate them. This special low phosphorus diet is continued for 3-6 days (it would seem logical to decrease further the phosphorus absorption by using aluminium hydroxide), by which time the serum phosphorus in the hyperparathyroid subject may have fallen to low levels, while the urine phosphorus has been little affected. In the normal subject, the serum phosphorus will have changed little, but the urine output should become extremely low.

The second test is, theoretically at least, a fundamental one. One of the basic actions of parathyroid hormone is believed to be that of reducing the capacity of the renal tubules to reabsorb phosphorus and so, other things being equal, to increase the urinary phosphorus. The test therefore measures the actual capacity of the tubules to reabsorb phosphorus. To do this, the serum phosphorus is elevated by intravenous injection of buffered phosphate, and the actual phosphate clearance is measured. This may then be related to creatinine clearance (or, more accurately, to the glomerular filtration rate as measured by inulin clearance); the phosphate clearance is higher than normal in hyperparathyroidism (the tubular reabsorbtion being less than normal).

The third test is that of calcium infusion. Here the serum calcium is artificially raised by the intravenous infusion of calcium gluconate (or similar saccharate). For some presently obscure reason, this manoeuvre usually causes a raising of the serum phosphorus in the normal subject by at least 2 mgm. per 100 ml. In the hyperparathyroid this rise is much less in extent.

Not very much experience has yet accumulated regarding

hierdie toetse nie, sodat ons ons tans maar grootliks moet verlaat op die herhaalde berekening van die serum-kalsium en -fosfor om 'n diagnose te bereik. Om verskeie redes is dit nie wenslik om die nek te ondersoek vir 'n moontlike adenoom van die byskildklier nie, maar in enkele gevalle is selfs dit toelaatbaar, bv. by pasiënte met ontwikkelende nierbeskadiging waar daar nog aan die diagnose getwyfel word selfs ná volledige en noukeurige ondersoek.

Op die gebied van oormatige byskildklierwerking was daar onlangs nog twee belangrike vorderings. 'n Hele paar voorbeelde van 'n familie-voorkoms van oormatige byskildklierwerking is gerapporteer.[3] By hierdie gevalle is die oormatige byskildklierwerking veroorsaak deur *veelvoudige* adenome in die paratiroïed, en daar kan ook adenome voorkom in die harsingslymklier (kleurwerende gewasse), en in die pankreas (gewasse van die eilandselletjies wat 'n oormaat insulien veroorsaak). Daar moet dus by elke geval van oormatige byskildklierwerking gesoek word vir spore van gewasse in hierdie ander endokrien-organe. Indien gewasse in hierdie organe gevind word, kan die geneesheer meer as een byskildkliergewas verwag, en die ander familielede van die pasiënt moet ook ondersoek word.

Ten slotte: Die voorkomssyfer van verskeie spysverteringsteurnisse by oormatige byskildklierwerking is ook bereken.[4] By sommige gevalle is 'n dundermsweer ook teenwoordig. Aan die ander kant kan oormatige byskildklierwerking ook sweer-nabootsende simptome veroorsaak; waarskynlik speel die volgehoue hiperkalsemie hier 'n rol. Die les wat hieruit geleer moet word is dat, by chroniese spysverteringsteurnisse sonder 'n duidelike oorsaak, die urine- en serum-kalsiumgehalte altyd bepaal moet word in geval oormatige byskildklierwerking aanwesig is.

1. Simpson, S. L. en Wilson, R. R. (1955): Brit. Med. J., **2,** 1283.
2. Chambers, E. L., Gordon, G. S., Goldman, L. en Reifenstein, E. C. (1956): J. Clin. Endocrinol., **16,** 1507.
3. Underdahl, L. O., Woolner, L. B. en Black, B. M. (1953): J. Clin. Endocrinol., **13,** 20.
4. St. Goar, W. T. (1957): Ann. Int. Med., **46,** 102.

these tests, so that our present main standby in diagnosis must still be the repeated estimation of serum calcium and phosphorus. An exploration of the neck 'in case' a parathyroid adenoma is present is not good practice for various reasons, but occasionally even this may be permissible in a patient where the diagnosis remains doubtful after full and careful examination, and in whom renal damage is developing.

Two other advances in knowledge concern hyperparathyroidism. Several instances of a familial incidence of hyperparathyroidism have been found.[3] In these cases the hyperparathyroidism is caused by *multiple* parathyroid adenomas, and, moreover, adenomas may be found also in the pituitary (chromophobe tumours) and in the pancreas (islet cell tumours which produce hyperinsulinism). In any case of hyperparathyroidism, therefore, evidence of tumours of these other endocrine organs should be sought. If found, then more than one parathyroid adenoma must be expected, and the rest of the family should be examined.

Finally the incidence of dyspepsia and other gastro-intestinal symptoms in hyperparathyroidism has been evaluated.[4] In some cases a duodenal ulcer is present; on the other hand symptoms like those of ulcer may be caused by the hyperparathyroidism—probably related to the continued hypercalcaemia. The moral of this is that in chronic dyspepsia of obscure origin, the urine and serum calcium should be estimated in case hyperparathyroidism is present.

1. Simpson, S. L. and Wilson, R. R. (1955): Brit. Med. J., **2,** 1283.
2. Chambers, E. L., Gordon, G. S., Goldman, L. and Reifenstein, E. C. (1956): J. Clin. Endocrinol., **16,** 1507.
3. Underdahl, L. O., Woolner, L. B. and Black, B. M. (1953): J. Clin. Endocrinol., **13,** 20.
4. St. Goar, W. T. (1957): Ann. Int. Med., **46,** 102.

THE PICKWICKIAN SYNDROME : ANOTHER HAZARD OF OBESITY

There have recently been several reports in the medical press concerning a syndrome of obesity, somnolence, polycythaemia and excessive appetite, with cyanosis, hypercapnia, and even right-sided heart failure without recognizable heart or lung disease.[1-4] As Burwell and his colleagues[4] point out, this association of features has been well known for a long time; it was particularly well described by Charles Dickens in *Pickwick Papers.* Dickens refers to 'A fat and red-faced boy in a state of somnolency'. He is later addressed as 'Young Dropsy', 'Young Opium-Eater' and 'Young Boa Constrictor'. The extraordinary degree of somnolence which may overcome such individuals even while engaged in conversation or actual muscular activity is illustrated further by Dickens:

'A most violent and startling knocking was heard at the door; it was not an ordinary double knock, but a constant and uninterrupted succession of the loudest single raps, as if the knocker were endowed with the perpetual motion, or the person outside had forgotten to leave off . . .

'Mr. Lowton . . . hurried to the door. . . . The object that presented itself to the eyes of the astonished clerk was a boy—a wonderfully fat boy— . . . standing upright on the mat, with his eyes closed as if in sleep. He had never seen such a fat boy, in or out of a travelling caravan; and this, coupled with the calmness and repose of his appearance, so very different from what was reasonably to have been expected of the inflictor of such knocks, smote him with wonder.

' "What's the matter?" inquired the clerk.

'The extraordinary boy replied not a word; but he nodded once, and seemed, to the clerk's imagination, to snore feebly.

' "Where do you come from?" inquired the clerk.

'The boy made no sign. He breathed heavily, but in all other respects was motionless.

'The clerk repeated the question thrice, and receiving no answer, prepared to shut the door, when the boy suddenly opened his eyes, winked several times, sneezed once, and raised his hand as if to repeat the knocking. Finding the door open, he stared about him with astonishment, and at length fixed his eyes on Mr. Lowton's face.

' "What the devil do you knock in that way for?" inquired the clerk angrily.

' "Which way?" said the boy, in a slow, sleepy voice.

' "Why, like forty-hackney-coachmen," replied the clerk.

' "Because master said I wasn't to leave off knocking till they opened the door, for fear I should go to sleep," said the boy.'

A patient of Burwell *et al.* was in the habit of playing poker once a week. On one occasion he was dealt a hand containing 3 aces and 2 kings, known, we believe, as a 'full house'. Since, however, the recipient of this good fortune then fell asleep, he was unable to obtain any advantage from it. A few days later he entered hospital.

Other clinical features of the Pickwickian syndrome include periodic breathing, twitching, cyanosis, and right ventricular hypertrophy with failure. Clubbed fingers have been seen.

Full investigations of pulmonary mechanics in these cases have ruled out a central lesion involving the respiratory centre as the cause of hypoxia and hypercapnia. They have shown that the increase in actual CO_2 pressure produced by prolonged exposure to high levels of carbon dioxide no longer causes the normal increase in respiration. The respiratory centre, apparently, has a reduced sensitivity, which, however, can be reversed by decreasing the CO_2 pressure to a normal level. The great reduction in vital capacity found in these patients is unassociated with any primary cardiac or pulmonary disease, and pulmonary arterio-venous shunt can also be ruled out, since alveolar ventilation is low rather than high and the arterial CO_2 tension is high rather than low.

It is believed that the extreme obesity leads to a low expiratory reserve volume and to a diminished functional residual capacity. In some way it also leads to shallow respiration and subnormal alveolar ventilation. The chest walls of the patients barely move with deep inspiration, perhaps because the rib cage is immobilized by the heavy fat pads as by a binder or cuirass.

Shallow breathing diminishes alveolar ventilation because each breath has first to fill the dead space before the alveoli are reached. The respiratory rate then increases, but this is entirely unable to compensate for the low alveolar ventilation, and carbon-dioxide retention results, together with reduced oxygenation of arterial haemoglobin. Shallow, periodic breathing may set in, with secondary polycythaemia, cyanosis, somnolence and twitching. The right heart is called upon to perform excessive work, against an increased pulmonary artery pressure and with an insufficient oxygen supply for its own musculature. True cor pulmonale results, with peripheral oedema, venous hypertension, hepatomegaly, right axis deviation, and even incomplete right bundle-branch block on the electrocardiogram. This is comparable to the state of affairs in the right heart strain caused by severe kyphoscoliosis unassociated with emphysema. All this has been shown to disappear after a reduction in weight has been achieved.

This syndrome thus illustrates another of the dangers of obesity. The obesity is caused by overeating, and cannot any longer be looked upon vaguely as a 'hypothalamic' disease because of its association with somnolence. The somnolence in this syndrome can be more physiologically explained by deficient gaseous exchange in the blood and also, perhaps, partly by the soporific effects of too much food.

1. Sicker, H. O., Ester, E. H., Kelser, G. A. and McIntosh, H. D. (1955): J. Clin. Invest., **34**, 916.
2. Auchincloss, J. R., Cook, E. and Renzetti, A. D. (1955): *Ibid.*, **34**, 1537.
3. Carrol, D. (1956): Amer. J. Med., **21**, 819.
4. Burwell, C. S., Rown, E. D., Whaley, R. D. and Bickelmann, A. G. (1956): *Ibid.*, **21**, 811.