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SINDROME BY VITAMIEN B12-GEBREK

Dit is noodsaaklik vir die behoorlike rypword van die rooi bloedselle dat daar 'n voldoende konsentrasie van vitamien B12 in die selle is. Hierdie vitamien kom hoofsaaklik in dierlike proteïene voor, en dit is slegs by 'n paar plantaardige voedselstowwe, soos grondboontjies en seewier, afgesonder. Ons liggame trek hierdie stof uit die voedsel wat ons eet en dit word uit die maagdermkanaal in die weefsels opgeneem indien 'n bloedvormende faktor (intrinsieke faktor) deur die maagslymvlies afgeskei word. As hierdie intrinsieke faktor ontbreek, ontwikkel daar megaloblastiese veranderings in die beenmurg en sirkulerende bloed. Die vol-ontwikkelde beeld van so 'n siekte word by Addisoniese kwaadaardige bloedarmoede gesien; hier word die intrinsieke faktor nie afgeskei nie en kom 'n histamien-vaste gebrek aan soutsuur in die maag voor weens verskrompeling van die maagslymvlies. Indien die tipiese kliniese verskynsels teenwoordig is tesame met megaloblastose van die beenmurg, is die diagnose maklik, en 'n gunstige reaksie op behandeling met vitamien B12 kan verwag word.

Dit blyk egter dat 'n gebrek aan vitamien B12 (sianokobalamien), wat goed reageer op behandeling met vitamien B12, ook kan voorkom waar daar *geen* bloedarmoede is nie. 'n Bekende voorbeeld hiervan is die subakute gekombineerde ontaarding van die rugmurg waarby die senuweeletsels oor die jare vererger, egter met normale vorming van rooi bloedliggaampies. Ook kom 'n vitamien B12-tekort voor by pasiënte wat vry suur in die maag afskei en geen tekort aan intrinsieke faktor het nie.

Die enigste betroubare metode om die vitamien B12-tekort direk te bereken is om die hoeveelheid beskikbaar in die liggaam te bepaal. Dit is moontlik gemaak deur die gebruik van die metodes van mikrobiologiese ontleding van die gehalte in die bloedserum.[1-3] Daar is nog 'n ander toets wat indirekte inligting verskaf van die (liggaam se) vermoë om vitamien B12 te absorbeer, nl. Schilling[4] se toets vir die opname van radioaktiewe vitamien B12, waar die urienuitskeiding gemeet word ná mondelikse toediening van die gemerkte kobalt. Gebrekkige absorpsie word aangetoon deur 'n lae gehalte in die urien.

Deur middel van hierdie metodes kan omvangryker navorsing gedoen word op die rol wat sianokobalamien by bloedarmoede en ander siekteverskynsels speel. Dit word algemeen aangeneem dat die normale serumhoogte by 'n volwasse mens tussen 150 en 900 $\mu\mu$g. per ml. is, met 'n gemiddelde hoeveelheid van 390 $\mu\mu$g. per ml. By kwaadaardige bloedarmoede is die gehalte 10-100—gemiddeld 50 $\mu\mu$g. per ml. Dit is moontlik dat die liggaam 'n reserwe

EDITORIAL

SYNDROMES IN VITAMIN B12 DEFICIENCY

An adequate concentration of vitamin B12 in the tissues is necessary for proper maturation of red blood-cells. It is contained mainly in animal proteins, and it has been identified in only a few vegetable foods, such as peanuts and seaweed. The substance is obtained from the food we eat, and it is absorbed into the tissues from the gastro-intestinal tract when a haemopoietic factor (intrinsic factor) is secreted by the mucosa of the stomach. When intrinsic factor is absent, megaloblastic changes will develop in the bone-marrow and circulating blood. The full-blown picture of such a condition is seen in Addisonian pernicious anaemia, in which there is failure of secretion of intrinsic factor and histamin-fast achlorhydria due to atrophy of the gastric mucous membrane. Given typical clinical appearances together with megaloblastosis of the bone-marrow, the diagnosis presents no difficulty and a successful response to treatment by vitamin B12 may be expected.

It has, however, become apparent that vitamin B12 (cyanocobalamin) deficiency, responding well to vitamin-B12 treatment, may occur in the absence of signs of anaemia. A well-known example of this is subacute combined degeneration of the cord, in which neurological defects may progress over a period of years with normal erythropoiesis; and there may be deficiency of the substance in some patients who secrete free acid in the stomach and have no lack of intrinsic factor.

The only reliable method of directly assessing vitamin-B12 deficiency is by measuring the amount available in the body and this was made possible by the introduction of methods of microbiological assay of the level in the blood serum.[1-3] Another test giving indirect information concerning capacity to absorb vitamin B12 is the Schilling[4] modification of absorption of radio-active vitamin B12, whereby the urinary excretion is measured after the oral administration of the labelled cobalt. Deficient utilization is revealed by a low level in the urine.

These techniques have widened the field of research in the part played by cyanocobalamin in the anaemias and other disease conditions. It is generally accepted that the normal adult serum level ranges from 150 to 900 $\mu\mu$g. per ml., with an average of 390 $\mu\mu$g. per ml. In pernicious anaemia the

van 2,000 μg. of meer het van hierdie stof, en dat die gebrek, waar dit voorkom, reeds voorafgegaan is deur 'n lang tydperk van verval. Maande of selfs jare kan verbygaan voordat die kritieke bodempunt bereik word. Pitney en Beard[5] het reekse-bepalings uitgevoer op 'n pasiënt wie se hele maag omrede kanker uitgesny was. Hulle het bevind dat die serumhoogte geleidelik gedaal het en dat dit eers na 8 maande die hoeveelheid van 110 $\mu\mu$g. per ml. bereik het.

Megaloblastiese bloedarmoede kan by 'n verskeidenheid siektes voorkom in gematige en tropiese klimate; idiopatiese steatorrhea en lusse en vernouings van die dunderm waarin die inhoud nie voortbeweeg nie, is voorbeelde hiervan. Mollin en Ross[6] het baanbrekerswerk gedoen op die hoeveelheidsbepaling van vitamien B12 in menslike serum, en in die loop van hulle werk het hulle by meer as 'n derde van die gevalle van steatorrhea lae gehaltes gevind binne skommelingsperke wat by kwaadaardige bloedarmoede verwag kan word. Dit was aangetoon dat pasiënte met subakute gekombineerde ontaarding, sonder bloedarmoede, die laagste gehaltes gehad het. Meynell *et al.*[7] het soortgelyke bevindings by steatorrhea en ook by streek-ileitis beskrywe, maar by verswerende colitis was daar geen vitamien B12-gebrek nie. Adams[8] het onlangs verslag gedoen oor 3 pasiënte wat bloot oor seer tonge gekla het. Daar was so te sê geen bloedarmoede nie, maar die B12-gehaltes was binne die perke wat by kwaadaardige bloedarmoede gevind word, en die pasiënte het besonder goed op behandeling met vitamien B12 gereageer.

In Suid-Afrika slaan die voorkomssyfer van kwaadaardige bloedarmoede by blankes ooreen met dié wat in Europa en Amerika aangetref word. Dit is blykbaar seldsaam by naturelle en Indiërs en dusver is slegs 3 gevalle gerapporteer. Adams[9] beskryf die geval van 'n manlike Zoeloe met makrosietanemie, megaloblastiese beenmurg, maagverskrompeling, en 'n serumgehalte aan B12 wat by kwaadaardige bloedarmoede verwag kan word.

Die meeste gevalle van megaloblastiese anemie by die Bantoe- en die Indiërbevolking staan in verband met swangerskap en die kraamtydperk, en die kondisie word goed beskryf in ons literatuur.[10–15] Die patogenese van die siekte word nog nie goed verstaan nie. Die meeste pasiënte skei vry suur af en reageer goed op behandeling met foliensuur, maar 'n paar herstel ná behandeling met groot dosisse vitamien B12. Adams[16] het gevind dat die serumgehalte aan vitamien B12 by die meeste gevalle binne normale perke is en verklaar dat hy ‚nog geen gevalle (gesien het) wat nie op foliensuur gereageer het by die afwesigheid van besmetting nie'. Aangesien dit so moeilik is om te bepaal wat dan juis die faktor is waaraan die liggaam gebrek ly, blyk dit dat 'n kombinasie van foliensuur en vitamien B12 die verkieslikste behandeling is. Adno[14] het omtrent 7 gevalle van hierdie gebreksindroom by welgevoede, blanke swanger vroue beskryf.

Foy *et al.*[17] klassifiseer die gevalle van nie-kwaadaardige anemie wat hulle in Oos-Afrika by naturelle beskryf in 2 groepe. Die eerste groep reageer op behandeling met penisillien òf op klein dosisse vitamien B12, en die serumgehaltes aan B12 is baie laag. Die tweede groep reageer alleenlik op mondelikse foliensuur en die B12-gehaltes is normaal. Dit word gemeen dat, by dié gevalle wat op penisillien reageer, die antibiotiese middel sekere organismes in die derm vernietig wat met die liggaam kompeteer om vitamien B12. Moontlik staan hierdie kondisie in verband met

level is 10-100, with an average of 50 $\mu\mu$g. per ml. It is possible that the body has a reserve of up to 2,000 μg. or more of the substance and that where deficiency occurs it follows a slow decline, and months or years may elapse before the critical minimum level is reached. Pitney and Beard[5] carried out serial estimations in a patient who had had a total gastrectomy for carcinoma and found that the serum level fell gradually and that only after 8 months had it dropped to 110 $\mu\mu$g. per ml.

Megaloblastic anaemia may occur in a variety of conditions in temperate and tropical climates; idiopathic steatorrhoea and stagnant loops and strictures of the small bowel are examples. Mollin and Ross,[6] in their pioneer work on the assay of vitamin B12 in human serum, found low values in more than one-third of cases of steatorrhoea, some in the range expected in pernicious anaemia. Patients with subacute combined degeneration but no anaemia were shown to have the lowest values. Meynell *et al.*[7] described similar findings in steatorrhoea and also in regional ileitis, but there was no vitamin-B12 deficiency in ulcerative colitis. Adams[8] has recently described 3 patients complaining merely of sore tongue. There was no appreciable anaemia, but B12 levels were in the range noted in pernicious anaemia and response to treatment with vitamin B12 was excellent.

In South Africa the incidence of pernicious anaemia in Europeans is similar to that found in Europe and America. It is apparently uncommon in the African and Indian populations and only 3 such cases have been reported. Adams[9] describes the case of a male Zulu who had a macrocytic anaemia, megaloblastic bone-marrow, gastric atrophy, and a serum-B12 level in the range to be expected in pernicious anaemia.

The majority of cases of megaloblastic anaemia in Bantu and Indian patients are associated with pregnancy and the puerperium, and the condition is well documented in the South African literature.[10-15] The pathogenesis of the condition is as yet uncertain. The majority secrete free acid and respond to treatment by folic acid, but a few recover after therapy with large doses of vitamin B12. Adams[16] finds the serum vitamin-B12 level to be within normal range in the majority of cases and states that he has 'not encountered failure to react to folic acid in the absence of infection'. In view of the difficulty of deciding which of the factors is deficient, the treatment of choice in this type of megaloblastic anaemia would appear to be a combination of folic acid and vitamin B12. Adno[14] has described some 7 cases in well-fed European women during the antenatal period.

The non-pernicious megaloblastic anaemias of Africans described in East Africa by Foy *et al.*[17] are classified by them into 2 categories. The first responds to treatment either by penicillin or small doses of vitamin B12 and the serum-B12 levels are very low. The second group responds only to folic acid by mouth, and vitamin-B12 levels are normal. It is thought that in the penicillin-responsive cases the antibiotic destroys organisms in the gut which compete with the body for vitamin B12. The condition is probably

die dieet, wat arm aan proteïen en ryk aan koolhidraat is. Maar dit is nog nie duidelik of dié dieet te min vitamien B12 en foliensuur bevat nie, òf of dit die ontwikkeling van bakteriese flora aanmoedig wat die behoorlike sintese en absorpsie van die vitamiene teenwerk nie.

Dit is reeds bewys dat 'n goeie persentasie van bejaarde pasiënte met 'n soutsuur-tekort (maar geen anemie nie) vitamien B12 swak absorbeer.[4] Pedersen *et al.*[18] het tydens soortgelyke studies in Denemarke die beenmurg van pasiënte met ligte hipochromiese anemie en achlorhydria bestudeer en gevind dat omtrent 15 persent 'n gedeeltelike of beginnende megaloblastose getoon het. Hulle stel voor dat ligte vitamien B12-gebrek té selde uitgeken word omdat die megaloblastiese neiging deur 'n ystertekort (dimorfies) gemasker kan word. As daar grade van vitamien B12-gebrek bestaan, soos hulle voorstel, wat vae simptome van agteruitgang toon soos seer tong, swakheid en geestesversteurings, is daar in sommige gevalle regverdiging vir geneeshere se aanspraak daarop dat inspuitings van vitamien B12, veral by bejaardes, 'n ,opknappende' uitwerking het.

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9. Adams, E. R. (1957): S. Afr. T. Geneesk., **31,** 633.
10. Cohen, L. (1953): *Ibid.*, **27,** 627.
11. Adams, E. B. en Wilmot, A. J. (1953): *Ibid.*, **27,** 1028.
12. *Idem.* (1956): Brit. Med. J., **2,** 398.
13. Patz., I. M. (1957): S. Afr. T. Geneesk., **31,** 384.
14. Adno., J. (1957): *Ibid.*, **31,** 10.
15. Nel, R. W. A. (1957): *Ibid.*, **31,** 192.
16. Adams, E. B. (1957): *Ibid.*, **31,** 324.
17. Foy, H., Kondi, A. en Manson-Bahr, P. E. C. (1955): Lancet, **2,** 693.
18. Pedersen, J., Lund, J., Ohlsen, A. S. en Kristensen, H. P. O. (1957): *Ibid.*, **1,** 448.

related to the diet, which is poor in protein and rich in carbohydrates. But it is not as yet clear whether the diet is deficient in vitamin B12 and folic acid, or encourages the growth of bacterial flora inimical to proper synthesis or absorption of the vitamins.

It has been shown that a fair proportion of elderly patients with achlorhydria but no anaemia absorb vitamin B12 poorly.[4] In parallel studies in Denmark, Pedersen *et al.*[18] examined the bone marrow of patients with mild hypochromic anaemia and achlorhydria and found that some 15% had a partial or incipient megaloblastosis. They suggest that mild vitamin-B12 deficiency is too seldom diagnosed because the megaloblastic tendency may be masked by iron deficiency anaemia (dimorphous). If, as they suggest, there are degrees of vitamin-B12 deficiency producing vague symptoms of ill-health, such as sore tongue, weakness and psychological disturbances, there would be some justification, in occasional cases, for the insistence by practitioners that injection of vitamin B12 has a 'tonic' effect, particularly in elderly patients.

1. Hutner, S. H., Provasoli, L., Stokstad, E. L. R., Hoffman, O. E., Belt, M., Franklin, A. L. and Jukes, T. H. (1949): Proc. Soc. Exp. Biol., **70,** 118.
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