South African Medical Journal
Suid-Afrikaanse Tydskrif vir Geneeskunde

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STOLLINGSTEENSTOWWE IN DIE BLOEDSOMLOOP

By pasiënte wat aan bloedingssiektes ly ontbreek daar moontlik in die bloed 'n faktor wat noodsaaklik is vir doeltreffende stolling. Ons kan dadelik aan voorbeelde hiervan dink. Daar is byvoorbeeld die afwesigheid van bloedplaatjies by siektes waarby hierdie plaatjies drasties verminder word, die gebrek aan bloedingbestrydende globulien by hemofilie, en die gebrek aan faktor 5 of faktor 7 hetsy as aangebore afwyking, hetsy as later ontstaande defek. Baie ander voorbeelde kan aangehaal word. In die meeste gevalle kan die stollingsabnormaliteit reggestel word deur die toevoeging van klein hoeveelhede normale bloed tot hierdie soort abnormale bloed, of selfs deur die toevoeging van een abnormale bloedsoort tot 'n ander soort abnormale bloed. Laasgenoemde geval word beskou as 'n wederkerige vergoeding vir gebreke, want elkeen van die abnormale bloedsoorte bevat betreklik baie van die faktor wat by die ander ontbreek.

By sekere siektes bestaan hierdie toestand nie. Die pasiënt kan 'n stollingsdefek en 'n kwaai bloedingssiekte hê. Maar nie alleen word die bloed slegs onvolkome gekorrigeer deur die toevoeging van normale bloed nie, maar die normale bloed word boonop abnormaal gemaak. Hierdie omstandighede dui gewoonlik op die aanwesigheid van 'n stollingsteenstof in die bloedsomloop. 'n Vergelykbare toestand sou bestaan as 'n stollingsremmende stof soos heparien *in vitro* bygevoeg word. In seldsame gevalle kan heparien-agtige werksaamheid selfs aangetoon word by natuurlik voorkomende siektes,[1, 2] of dit kan voorkom ná die gebruik van stikstofmosterd of ioniserende bestralings.[3] Maar die stollingsteenstof is in die meeste gevalle nie heparien, of selfs heparien-agtig, nie.

Daar is drie groepe siektetoestande wat verantwoordelik is vir die meeste gevalle waar stollingsteenstowwe in die bloed voorkom:[3–6] (*a*) kompliserende kondisies by hemofilie en christmas-siekte; (*b*) kondisies na swangerskap; (*c*) 'n verskeidenheid slepende siektes.

Voorbeelde van hierdie komplikasie by hemofilie en christmas-siekte word vandag meer dikwels as in die verlede uitgeken. Dit is ongetwyfeld deels te danke aan beter diagnose, en waarskynlik ook deels aan die groter gebruik van bloed- of bloedplasma-oortappings. Daar is reeds aanspraak gemaak daarop,[7] en dit is moontlik bevestig,[8] dat natuurlik voorkomende hemofilie geheel en al òf gedeeltelik te wyte is aan 'n oormaat van 'n stof wat 'n stollingsremmende werking het. Maar baie

EDITORIAL

CIRCULATING ANTICOAGULANTS

Patients suffering from bleeding diseases may lack a factor in their blood which is necessary for adequate coagulation. Examples of this readily spring to mind. One may mention the absence of blood platelets in thrombocytopenic states, the deficiency of anti-haemophilic globulin in haemophilia, and the lack of factor 5 or factor 7 either as a congenital anomaly or an acquired defect. Many more examples could be quoted. The coagulation defect can, in most cases, be corrected by the addition of small proportions of normal blood to this kind of abnormal blood, or even by the addition of one abnormal blood to a different variety of abnormal blood. The latter instance is regarded as a mutual correction of defects, since each of the abnormal bloods contains a relative abundance of the factor which is lacking in the other.

In certain diseases this state of affairs does not exist. The patient may have a coagulation defect and a severe haemorrhagic state. Yet not only is the blood not fully corrected by the addition of normal blood but the normal blood is rendered abnormal. These circumstances usually imply the presence of a circulating anticoagulant. A somewhat comparable state of affairs would exist if an anticoagulant substance such as heparin were added *in vitro*. On rare occasions, heparin-like activity may even be demonstrated in naturally occurring disease[1,2] or may follow the use of nitrogen mustard or ionizing radiations.[3] But in most cases the anticoagulant is not heparin or even heparin-like.

Three groups of conditions account for the bulk of cases in which circulating anticoagulants have been encountered:[3–6] (*a*) conditions complicating haemophilia and christmas disease; (*b*) conditions following pregnancy; and (*c*) a variety of chronic diseases.

Instances of this complication of haemophilia and christmas disease are being encountered more frequently than in the past. This is no doubt due in part to better diagnosis and also probably to the greater use of blood or plasma transfusion in those diseases. It has been claimed,[7] in

sensitiewe toetse is nodig om hierdie stof aan te toon. Die stollingsteenstof in die bloed, wat by hemofilie en by ander siektes ontwikkel, toon klinies en in die laboratorium treffende afwykings. Dit kom slegs nou en dan voor, en is klaarblyklik 'n teenliggaam wat ontstaan as gevolg van die antigeen-prikkeling van die bloedingremmende globulien aanwesig in oorgetapte bloed. Dit verduidelik dan ook sy teenwoordigheid in die gammaglobulien-bestanddeel in die bloed en die feit dat die neerslagtoetse positief was by sommige gerapporteerde gevalle. Dit is proefgewys by konyne opgewek.[9] Gevalle wat gedurende of kort ná swangerskap voorkom is ook moontlik te wyte aan 'n immunologiese meganisme. Daar is selfs 'n verslag oor 'n geval[10] waar die pasiënt gedurende haar eerste en tweede swangerskap 'n stollingsteenstof ontwikkel het, en haar tweede kind het by geboorte 'n soortgelyke afwyking van die stollingsmeganisme getoon. Die stollingsteenstof kon 77 dae lank in die kind se bloed aangetoon word, wat 'n sterk aanduiding was dat die teenliggaampies deur die plasenta uitgewissel is. Stollingsteenstowwe word ook aangetref by pasiënte wat ander tekens van 'n immunologiese steuring toon, soos die aanwesigheid van rooi bloedsel outo- en iso-agglutiniene en 'n positiewe Coombs-toets soos by sommige gevalle van verspreide lupus erythematosus (DLE) en polyarteritis nodosa.[3] Stollingsteenstowwe is tewens glad nie ongewoond by DLE nie,[11] en 'n spesiale kombinasie van stollingsdefekte by hierdie siekte word selfs beskryf.[12] Maar die immunologiese meganisme kan nie op grond van ons huidige kennis geblameer word vir alle gevalle van stollingsremmende stowwe in die bloedsomloop nie, want hierdie stowwe is blykbaar reeds aangetref by oënskynlik gesonde persone en by pasiënte met teringagtige klieraandoenings, vergrote limfknope weens reaktiewe oormatige groei van onbekende oorsake, propvorming in die hartspier, slepende nierontsteking, sifilis en ander siektes.[4]

As die siekte eers vermoed word, is dit nie baie moeilik om die diagnose in die laboratorium te bevestig nie. Die een-stadium protrombien-tyd is gewoonlik normaal omdat die meeste van hierdie stollingsremmende stowwe nie vóórgevormde tromboplastien affekteer nie, maar eerder gedurende die vorming van bloed-tromboplastien inwerk. Die stollingstyd is gewoonlik lank, en mengsels van die pasiënt se volle bloed met normale volle bloed neem langer as gewoonlik om te stol. Dit kan dikwels ook aangetoon word by mengsels van sitraat- of oksalaatplasma's van pasiënte met normale bloedwei wat op dié manier behandel is, maar ook hier kan baie ongerymdhede voorkom. By sommige pasiënte kon die stollingsteenstowwe slegs by plasma waarby kalsium weer toegevoeg is gedemonstreer word en nie by volle bloed nie;[13] die stollingsteenstowwe kan ‚verdwyn' as die bloedwei nie dadelik getoets word nie,[14] of kan slegs bespeur word in plasma wat min bloedplaatjies bevat.[4] Soms kan die stollingsteenstof op kamertemperatuur aangetoon word en nie op liggaamstemperatuur nie.[15]

Dit is soms moontlik om deur middel van die protrombien-verbruikingstoets afwykings te demonstreer wat nie na vore kom wanneer die stollingstye van bloedmengsels getoets word nie.[16] Die tromboplastien-

fact, and possibly confirmed,[8] that naturally occurring haemophilia may in whole or in part be due to excess of an anticoagulant-like substance. But this substance requires very sensitive tests for its demonstration. The circulating anticoagulant which develops in these haemophilic cases and in other patients produces striking clinical and laboratory anomalies. It occurs only in occasional cases and is apparently an antibody resulting from the antigenic stimulus of the anti-haemophilic globulin present in the transfused blood. This explains its presence in the gamma-globulin fraction of blood and the finding of positive precipitin tests in some of the recorded cases. It has been reproduced experimentally in rabbits.[9] Cases occurring during or shortly after the termination of, pregnancy may also possibly be ascribed to an immunologic mechanism. A case has even been described[10] where a patient developed an anticoagulant during the first and second pregnancy and her second child was born with a similar abnormality of the coagulation mechanism. The anticoagulant was demonstrable in the child's circulation for 77 days, strongly suggesting transplacental transfer of antibodies. Anticoagulants are also found in patients showing other indications of an immunologic disturbance, such as the presence of red-cell autoagglutinins and iso-agglutinins, and a positive Coombes test, as in some cases of disseminated lupus erythematosus (DLE) and polyarteritis nodosa.[3] In fact circulating anticoagulants are not at all uncommon in DLE[11] and even a special combination of coagulation defects has been described in this condition.[12] But the immunologic mechanism cannot as yet be blamed for all cases with circulating anticoagulants since they have been said to have been encountered in apparently healthy people and in patients with tuberculous lymphadenopathy, enlarged lymph-nodes due to reactive hyperplasia of unknown origin, myocardial infarction, chronic nephritis, syphilis and other diseases.[4]

Once the condition has been suspected it is not very difficult to obtain laboratory confirmation. The one-stage prothrombin time is usually normal since most of these anticoagulants do not affect preformed thromboplastin, but act rather during the elaboration of blood thromboplastin. The coagulation time is commonly prolonged, and mixtures of the patient's whole blood with normal whole blood give coagulation times which are longer than normal. This can often also be shown with mixtures of citrate or oxalate plasma from the patient with normal plasma thus treated, but many anomalies occur. In some patients the anticoagulants were only demonstrable with recalcified plasma and not with whole blood;[13] anticoagulants may 'disappear' if the plasma is not tested immediately[14] or may only be detected in platelet-poor plasma.[4] Sometimes the anticoagulant may be demonstrable at room temperature and not at body temperature.[15] It may be possible to demonstrate abnormalities by means of the pro-

vormings-toets[4] kan moontlik die afwyking aantoon wanneer ander metodes nie daarin slaag nie, maar selfs hierdie toets is nie altyd onfeilbaar nie. Die belangrikste element by die diagnose is 'n sterk vermoede dat die pasiënte aan hierdie siekte ly.

Die behandeling is moeilik. Waar dit tesame met hemofilie voorkom, verbeter die kondisie gewoonlik mettertyd mits bloedoortappings vermy kan word. Soms kan 'n massale oortapping 'n pasiënt deur 'n krisis help, maar dit is moontlik dat die eintlike patologiese toestand vererger sal word. Sommige gevalle wat ná swangerskap voorkom kan baie lank duur (soms tot 13 jaar), terwyl ander binne 'n jaar of twee verbeter. Gevalle wat by 'n algemene siekte voorkom, verg behandeling vir daardie siekte, maar gewoonlik word die bloedingssiekte nie juis daardeur beïnvloed nie. Die adrenokortikotrofiese hormoon (ACTH), kortisoon en prednisoon is almal reeds gebruik, maar die resultate was meestal onbevredigend. Moontlik sal hulle doeltreffender wees by pasiënte wat aan verspreide lupus erythematosus of polyarteritis nodosa ly. Skommelings in die toestand kom egter ook vanself voor, en die verbetering word dan toegeskryf aan die behandeling wat toevallig op daardie tydstip toegepas word. Die meeste wat 'n mens kan verwag is om 'n behandelingsmiddel of metode uit te vind wat die pasiënt aan die lewe sal hou totdat verbetering spontaan intree.

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2. Speer, R. J., Hill, J. M., Maloney, M. en Roberts, A. (1955): J. Lab. Clin. Med., **45,** 730.
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9. Richards, M. D. en Spaet, T. H. (1956): Blood, **11,** 473.
10. Frick, P. G. (1953): *Ibid.*, **8,** 598.
11. *Idem* (1955): *Ibid.*, **10,** 691.
12. Bonnin, J. A., Cohen, A. K. en Hicks, N. D. (1956): Brit. J. Haemat, **2,** 168.
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14. Hougie, C. en Fearnley, M. E. (1954): Acta Haemat., **12,** 1.
15. Mueller, J. F., Ratnoff O. en Heinle, R. W. (1951): J. Lab. Clin., Med., **38,** 1.
16. Quick, A. J. Daniels, E. R. en Hussey, C. V. (1954): *Ibid.*, **44,** 94.

thrombin-consumption test which are not obvious when coagulation times of blood mixtures are tested.[16] The thromboplastin-generation test[4] may demonstrate the abnormality when other methods fail, though even this is not infallible. The most important element in the diagnosis is a high index of suspicion of the existence of the condition.

Treatment is not easy. Cases occurring in haemophilia generally subside in time provided transfusion can be avoided. Occasionally a massive transfusion may carry the patient through a crisis but this might conceivably aggravate the underlying pathological state. Cases following pregnancy may persist for long periods of time (even up to 13 years). Others have improved in a year or two. Cases occurring with systemic disease require treatment for that disease but this has very little effect on the haemorrhagic state in most cases. Adrenocorticotrophic hormone (ACTH), cortisone and prednisone have all been tried, but usually the results are disappointing. They may conceivably be more effective in patients with disseminated lupus erythematosus or polyarteritis nodosa. Spontaneous fluctuations also occur and improvement may be ascribed to whatever therapy is being used at any one time. The best that can usually be hoped for is to find some treatment that will keep the patient alive until a spontaneous remission occurs.

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