Biochemical markers in dementia

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Chapter 7

7.1
Nederlandse samenvatting

Adapted from "Een heldere kijk op dementie." N.A. Verwey. HMF Nr.3:2009;28-29

Dementie is een ziektebeeld dat zich kenmerkt door een progressieve achteruitgang van het geestelijk functioneren (meestal begint dementie met geheugenstoornissen). Het uitvoeren van allerlei dagelijkse handelingen/ vaardigheden is dan gestoord, met als gevolg dat het dagelijks functioneren van de patiënt belemmerd wordt.

In Nederland hebben 270.000 mensen dementie, hiervan zijn 12.000 mensen jong dementerend (< 65 jaar). Als gevolg van de vergrijzing zal het aantal mensen met dementie, de komende decennia, stevig toenemen naar meer dan een half miljoen in 2040. Na het stellen van de diagnose, leven patiënten met dementie gemiddeld 8 jaar. Het ziekteproces gaat gepaard met progressieve en ernstige klachten waarbij in toenemende mate de patiënt afhankelijk en zorgbehoevend wordt.

Helaas is er op dit moment geen genezing mogelijk met als gevolg dat dementie als ziekte een enorm beslag legt op ons gezondheidstelsel. Vanwege dit toekomstperspectief wordt er veel onderzoek gedaan naar dementie en de verwachting is dan ook dat in de nabije toekomst mogelijkheden voor therapie en preventie zich zullen ontwikkelen en uitbreiden. Vele muizenstudies en enkele onderzoeken met patiënten hebben laten zien dat therapieën gebaseerd op vaccinaties (passieve en actieve) zeer bemoedigend zijn. Om deze therapeutische mogelijkheden uit te breiden en te toetsen is vroege diagnostiek noodzakelijk. Immers hoe eerder bij patiënten een behandeling gestart kan worden, hoe beter.

De meeste voorkomende vorm van dementie is de ziekte van Alzheimer (AD) (70% van alle dementie patiënten). De diagnose wordt nu gesteld o.b.v. klinische criteria en met behulp van aanvullend onderzoek (beeldvorming, neuropsychologisch en neurofysiologisch onderzoek). Bij pathologisch hersenonderzoek worden bij patiënten met AD, amyloid plaques en 'tangles' gevonden, die de basis vormen voor de concentratie van drie eiwitten in liquor (CSF): amyloid-beta 1-42 (Aβ42), totaal tau (Tau) en gefosforyleerd tau op threonine 181 (P-Tau) De laatste jaren is gebleken dat deze drie biomarkers in CSF een bijdrage kunnen leveren bij de vroege diagnostiek van dementie.

Patiënten die wel objectiveerbare geheugenklachten hebben, maar nog volledig zelfstandig kunnen functioneren (zijn dus niet dement) worden ' Mild cognitive impairment ' (MCI) patiënten genoemd. Vijftig procent van de MCI-patiënten zal na 4 jaar dementie ontwikkelen. Ten aanzien van een eventuele behandeling, is het van groot belang om te kunnen voorspellen welke MCI-patiënten dementie zullen ontwikkelen, en welke niet. Nu is deze voorspelling met de huidige aanvullende onderzoeken (beeldvorming, neuropsychologisch onderzoek en neurofysiologisch onderzoek) lastig.

De afgelopen jaren heeft de bepaling van de concentraties van Aβ42, Tau and P-Tau in CSF hierin al meerwaarde aangetoond. Verschillende onderzoeksgroepen hebben

gevonden dat MCI-patiënten met een afwijkend biomarker profiel (laag Aβ42; hoog Tau; hoog Ptau) een grotere kans hebben om dementie te ontwikkelen. Verder lijken CSF biomarkers beter in staat, in vergelijking met beeldvorming zoals MRI scans, om eerder in het ziektebeloop te kunnen voorspellen of een MCI-patiënt AD zal ontwikkelen. Dit schept mogelijkheden om patiënten met cognitieve klachten meer duidelijkheid te geven over de mogelijkheid van de ontwikkeling van dementie. Maar misschien nog belangrijker, in de toekomst, zijn de MCI-patiënten met een afwijkend biomarkerprofiel de kandidaten die mogelijk baat hebben bij een specifieke anti-alzheimertherapie.

Vanwege de hierboven gevonden resultaten wordt er internationaal gepleit voor de introductie van de CSF bepalingen in het diagnostisch proces. Toch zijn er een aantal belangrijke zaken die dit moeilijk maken. Op dit moment zijn er nog te veel verschillen tussen laboratoria om standaard-afkapwaarden voor Aβ42, Tau en Ptau op te stellen. Het meten van deze eiwitten is lastig en elk laboratorium gebruikt daarom zijn eigen criteria. Samenwerkingsverbanden tussen diverse laboratoria in Europa en VS worden momenteel opgezet om de tests evenals het afname en verwerkingsprotocol van CSF te standaardiseren. Naast deze standaardisatie problemen, zijn de meetsystemen (om deze eiwitten te meten) niet solide genoeg. Op lab niveau wordt dus nu gewerkt aan het verbeteren van deze meetsystemen.

De verwachting is dat in de komende jaren deze technische problemen opgelost worden en dat er meer therapeutische mogelijkheden voor handen zijn. Dan zullen deze biomarkers hoogstwaarschijnlijk opgenomen worden in het diagnostisch proces, dit maakt het makkelijker om AD patiënten in een vroeg stadium te diagnosticeren (wat sowieso ook een voordeel is t.a.v. informatie, advies en begeleiding voor/van de patiënt), wat een groot voordeel is bij eventuele interventie.

Hopelijk zal dit vroeg opsporen van patiënten leiden tot het vertragen (het opschuiven van de leeftijd van onset met 5 jaar geeft een 50% reductie van de prevalentie) danwel genezing van dementie.

7.2
Dankwoord

Graag wil ik iedereen bedanken die mij geholpen heeft bij het maken van dit proefschrift. Allereerst wil ik alle patiënten bedanken. Zonder hun medewerking was dit wetenschappelijk onderzoek niet mogelijk geweest.

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7.3
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7.4
CV

Nicolaas Arthur was born the 18th of September 1976 in Leeuwarden, The Netherlands. After an elementary education in Calabria, a region in the southern part of Italy, he moved, when he was twelve years old, to The Netherlands.

In 1997 he graduated from Mencia de Mendoza Lyceum in Breda and decided to go to Medical School. As he was not admitted to Medical School in 1997 (because of the lottery system), he started with Pharmaceutical studies at Utrecht University. In 1998, he won the lottery and he started Medical School at the Utrecht University (from September 1998 to April 2005).

During his study he worked at the pulmonary department (UMCU and WKZ, Utrecht, The Netherlands) building databases for Cystic Fibrosis research and performed 1½ year research in the "assessment of cognition" in Parkinson's Disease at the Neurology department (LUMC, Leiden, The Netherlands). This resulted in 2003 in his first co-authorship in an internationally peer reviewed magazine and he continued his research in movement disorders for 5 months at the Rush University (Chicago, Illinois, USA).

After one year working as a neurology physician, in may 2006 he started his research project at the Alzheimer centre, department of Neurology and Clinical chemistry (VUMC, Amsterdam, the Netherlands), supervised by Prof. Dr. P. Scheltens and Prof. Dr. M.A. Blankenstein, which resulted in this thesis. During his research project, he participated in outpatient care at the Alzheimer Centre and he worked at the first aid for the Neurology department (VUMC, Amsterdam, The Netherlands). Since November 2009 he started his specialist registrar neurology training at the Neurology department (VUMC, Amsterdam, The Netherlands).

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