PRION DISEASES: AN OVERVIEW

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PRION DISEASES: AN OVERVIEW

WHAT ARE THEY?

WHY DO THEY HAPPEN?

HOW DO WE DIAGNOSE THEM?

HOW MIGHT WE TREAT THEM?

AND ALONG THE WAY: SOME OF THE HISTORY
VARIOUS FORMS OF CJD
SOME RARE GENETIC DISEASES
VPSPr
KURU
WHAT IS COMMON TO ALL THESE DIFFERENT FORMS OF ILLNESS?

ALL OF THEM:

BRAIN DISEASES

PROGRESSIVE & FATAL

SIMILAR PATHOLOGY: ‘NEURODEGENERATIVE’

RELATED TO A SPECIFIC PROTEIN ABNORMALLY

POTENTIALLY TRANSMISSIBLE*

*Generally only in certain specific circumstances
IN THE PAST:
DISEASES OFTEN NAMED AFTER PEOPLE

Hans Creutzfeldt          Alfons Jakob

CREUTZFELDT-JAKOB DISEASE:
THE COMMONEST HUMAN PRION DISEASE

1920s

GERSTMANN STRÄUSSLER SCHEINKER SYNDROME
A GENETIC HUMAN PRION DISEASE

1936
DESCRIPTIVE NAMES THEN BECAME POPULAR

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES
FIRST EXPERIMENTAL TRANSMISSION OF CJD 1968

Gibbs
Gajdusek
Asher
Alpers
Beck
Daniel
Matthews
THEN IN THE 1980s

PRION PROTEIN, ITS GENE
& THEIR ROLE IN THESE DISEASES
IDENTIFIED

Prusiner & Others
THE MODERN ERA:
A NAME REFLECTING THE PROTEIN UNDERPINNING

PRION DISEASES
PROTEINS: COMPLEX CHEMICAL STRUCTURES

~50,000 PROTEINS IN HUMAN BODY

STRUCTURAL ROLES

FUNCTIONAL ROLES

THEIR SHAPE (THEIR FOLDING) VERY IMPORTANT
PRION DISEASES

INVOLVE ABNORMALITY IN A SPECIFIC PROTEIN:
THE PRION PROTEIN

NORMAL PRION PROTEIN
FOUND IN MANY ANIMALS
FOUND IN MANY TISSUES

IMPORTANT
BUT
PRECISE FUNCTION?
PRION DISEASES

DISEASES IN WHICH THE PRION PROTEIN UNDERGOES A CHANGE IN CONFORMATION: ABNORMAL FINAL STRUCTURE
ABNORMAL PRION PROTEIN

ACCUMULATES
AGGREGATES
DEPOSITED IN TISSUE
WHAT MAKES HUMANS HUMAN?

OUR BRAINS

AND ITS MILLIONS OF NEURONES

CONNECTED ELECTRICALLY IN NETWORKS
THE FUNDAMENTAL DISEASE QUESTION:

WHAT CAUSES NEURONAL DYSFUNCTION & LOSS?

OUR UNDERSTANDING OF THIS IS INCOMPLETE & UNCERTAIN
IN PARTICULAR….

DEPOSITION OF AGGREGATED ABNORMAL PRION PROTEIN

Precise Relationship?

NEURONAL LOSS
ABNORMAL PRION PROTEIN: CONVERSION NOT ONE STEP

INTERMEDIATE FORMS MAY BE MOST IMPORTANT IN RELATION TO NEURONAL LOSS & INFECTIVITY
WHY DOES THIS HAPPEN?
3 BROAD REASONS

1: GENETIC PROBLEM: Abnormal gene-Abnormal Protein
2: INFECTION: Enters & causes change
3: CHANCE: Random Protein Production Mistake
   Mistake in Protein Quality Control
MAIN DISEASE TYPES

GENETIC PRION DISEASE

INHERITED MUTATIONS
50:50 CHANCE OF INHERITENCE

CLINICAL COURSE VARIABLE
DEPENDING, IN PART, ON THE PARTICULAR MUTATION
MAIN DISEASE TYPES

IATROGENIC CJD

ACCIDENTALLY TRANSMITTED PERSON-TO-PERSON
BY MEDICAL/SURGICAL PROCEDURES

MOST CASES PAST EXPOSURE TO
Growth Hormone
Dura Mater Grafts
MAIN DISEASE TYPES

VARIANT CJD

ORIGIN: DIETARY CONTAMINATION WITH BSE
MOST in UK
NO LIVING CASES IN WORLD AT THIS MOMENT

HAS OCCASIONALLY BEEN TRANSMITTED
PERSON-PERSON BY BLOOD
MAIN DISEASE TYPES

SPORADIC CJD

WORLDWIDE
COMMONEST HUMAN PRION DISEASE

MOSTLY MIDDLE AGED & ELDERLY

OFTEN RAPID PROGRESSION
A NOTE ABOUT TERMINOLOGY

**PRNP**

The NORMAL human gene that produces Prion Protein
*Mutations of it: Genetic Disease*

**PRION PROTEIN**

**PrP**

A protein

**PrPC**

The NORMAL Prion Protein we all have

**PrPSc**

The ABNORMAL Prion Protein in disease
That aggregates and is deposited in tissues

**PrP**

ABNORMAL Prion Protein forms intermediate
between PrPC and PrPSc

**PrPRES**

The Resistant Core of ABNORMAL Prion Protein

**The PRION**

Prion

The infectious particle: Composed entirely or mostly of abnormal PrP
DIAGNOSIS OF HUMAN PRION DISEASE

THINK OF IT AS A POSSIBILITY

EXCLUDE OTHER POSSIBILITIES

TESTS THAT SUPPORT THE DIAGNOSIS

PATHOLOGY
DIAGNOSIS OF HUMAN PRION DISEASE

THINK OF IT AS A POSSIBILITY

Rare: May have no knowledge/experience

But a competent clinician
Should recognize a serious illness
Should know how to seek advice
EXCLUDE OTHER POSSIBILITIES

A very important fact:

Prion disease often presents non-specifically
May be other much more likely diagnoses
May be other *treatable* diagnoses
DIAGNOSIS OF HUMAN PRION DISEASE

EXCLUDE OTHER POSSIBILITIES

Many Tests:
Not initially specifically directed at Prion Disease
But at excluding other possibilities
Even ones that can support a Prion Disease Diagnosis
[eg: Brain MR, Spinal Fluid Analysis]
DIAGNOSIS OF HUMAN PRION DISEASE

TESTS THAT SUPPORT THE DIAGNOSIS

Since the 1980s: Huge Progress
THE DIAGNOSTIC PROCESS

IN THE PAST

CLINICAL DIAGNOSIS RESTED MOSTLY ON:

ESSENTIALLY NON-SPECIFIC TESTS

NOT RELATED TO BASIC DISEASE MECHANISMS
Seeing Suspect Cases in 1980
BEFORE Prion Protein

CLINICAL FEATURES

EEG

CT Brain:
excluding some other diagnoses
But no positive support for diagnosis
ESSENTIALLY NON-SPECIFIC TESTS
NOT RELATED TO BASIC DISEASE MECHANISMS

EEG

BRAIN MRI

CSF 14-3-3

THE RELEVANT ABNORMALITIES CAN BE SEEN IN OTHER DISEASES
UTILITY: DEPENDS HEAVILY ON CLINICAL CONTEXT
For a While,

WE \textbf{HAVE} HAD
3 ESSENTIALLY SPECIFIC TESTS

One:

\textbf{DETECTION OF GENETIC MUTATION}

\textbf{IN}

\textbf{GENETIC PRION DISEASES}
For a While,

WE HAVE HAD
3 ESSENTIALLY SPECIFIC TESTS

Two:

NEUROPATHOLOGICAL DIAGNOSIS 
REQUIRING BRAIN TISSUE

AT AUTOPSY: Diagnosis only after death

BY BRAIN BIOPSY: Not undertaken lightly
For a While,

WE HAVE HAD TWO ESSENTIALLY SPECIFIC TESTS

Three:

DETECTION OF PrP$^{Sc}$ in TONSIL BIOPSY

BUT: RELEVANT ONLY IN VARIANT CJD
BUT IN THE LAST FEW YEARS:

A NUMBER OF NON-INVASIVE ESSENTIALLY SPECIFIC TESTS RELATED TO BASIC DISEASE MECHANISMS
ESSENTIALLY SPECIFIC TESTS:

DETECTION OF ABNORMAL PRION PROTEIN

DETECTION OF PrP$^\text{Sc}$

STANDARD METHODS OF DETECTION
DETECT ONLY HIGH LEVELS OF PrP$^\text{Sc}$

IN CJD (other than vCJD):
HIGH LEVELS ARE IN BRAIN
[LOW LEVELS CAN BE PRESENT]
ESSENTIALLY SPECIFIC TESTS:

DETECTION OF ABNORMAL PRION PROTEIN

But detection methods would work if

LOW LEVELS INCREASED

USING

AMPLIFICATION TECHNIQUES
AMPLIFICATION TECHNIQUES HAVE BEEN DEVELOPED ESSENTIALLY BASED ON AUTO-CATALYTIC CONVERSION OF PRION PROTEIN
AMPLIFICATION

SAMPLE

PrPSc

AMPLIFICATION

AMPLIFY THE AMOUNT SO BECOMES DETECTABLE BY AVAILABLE METHODS

Add PrPC
TWO BASIC PrP\textsuperscript{Sc} AMPLIFICATION TECHNIQUES

PMCA
PROTEIN MISFOLDING CYCLIC AMPLIFICATION

RT-QuIC
REAL-TIME QUAKING-INDUCED CONVERSION

[SOME REFINEMENTS OF THESE METHODS]
PrP^Sc AMPLIFICATION METHODS HAVE BEEN USED ON:

- SPINAL FLUID
- BLOOD
- URINE
- SKIN (BIOPSY)
- NASAL BRUSHINGS
PrPSc AMPLIFICATION TESTS IN CLINICAL DIAGNOSIS
NOTE I

TECHNIQUES TEND TO BEHAVE DIFFERENTLY IN DIFFERENT PRION DISEASES

CSF SPORADIC CJD: RT-QuIC
CSF VARIANT CJD: PMCA
PrPSc AMPLIFICATION TESTS IN CLINICAL DIAGNOSIS

NOTE II

A NUMBER OF RESEARCH DEVELOPMENTS

BUT

FEW YET PROPERLY EVALUATED

IN ROUTINE CLINICAL SETTINGS
THE BEST STUDIED: CSF RT-QuIC in SPORADIC CJD

CSF using RT-QuIC

NOW A STANDARD CLINICAL TEST

In the UK*:
Sensitivity 95+%
Specificity ~100%

*Different centres use slightly different techniques
TESTS IN PRACTICE

NO MATTER HOW TECHNICALLY GOOD THEY ARE

THEY NEED TO BE USED
BY AN APPROPRIATE CLINICIAN
IN AN APPROPRIATE PERSON
AT AN APPROPRIATE TIME

THEY REMAIN PART OF THE CLINICAL PROCESS

They cannot REPLACE the whole clinical process
FOOTNOTE:
IF PrP\textsuperscript{Sc} IS DETECTABLE IN BLOOD, URINE & SKIN IS IT A RISK TO OTHERS?

GENERALLY PRESENT AT LOW LEVELS

DETECTING ABNORMAL PrP IS NOT NECESSARILY DETECTING INFECTIVITY

INFECTION REQUIRES INFECTIVITY \textbf{AND} AN EFFECTIVE MEANS OF TRANSMISSION

INFECTIVITY IN EXPERIMENTS IS NOT NECESSARILY NATURAL INFECTION RISK

NO EVIDENCE OF ‘ORDINARY’ INFECTION WITH HUMAN PRION DISEASES EVEN WITH INTIMATE PERSONAL CONTACT
Through the diagnostic maze

Presentation

Final Diagnosis

Patient/Family View  Looks Obvious
Presentation was Typical of CJD
Through the diagnostic maze

Presentation

Medical View

Final Diagnosis

Not Obvious

Presentation Typical of many things
Through the diagnostic maze

Presentation

Final Diagnosis

Potentially Treatable
Through the diagnostic maze

Frustratingly & agonisingly:
This process takes time.....but time is sometimes a necessary part of the process
DIAGNOSIS OF HUMAN PRION DISEASE

PATHOLOGY IS THE FINAL DEFINITIVE TEST

BUT

A VERY CONFIDENT CLINICAL DIAGNOSIS IS POSSIBLE IN MANY CASES
For example: Antibody against PrP\textsuperscript{C} to deplete it
For example:
Small molecules
That interfere with this process

INTERMEDIATE FORMS

PROCESS OF NEURONAL DEATH
UNDERSTANDING PROCESSES OF NEURONAL DEATH

PROBABLE EARLIEST CHANGES IN SYNAPSES

EXPERIMENTAL EVIDENCE THAT THESE EARLY CHANGES ARE REVERSIBLE
A NOTE OF CAUTION: TWO TREATMENT SITUATIONS

CLINICAL ILLNESS

TREATMENT FOR PEOPLE ALREADY ILL

MAY WELL BE TOO LATE

Eg of AD TRIALS

PREVENTION

TREATMENT BEFORE ILL
Eg GENETIC MUTATION CARRIERS
RETURN TO THE FOLD
BACK TO THE FUTURE

ALZHEIMER’S
MOTOR NEURONE DISEASE
PARKINSON’S

COULD THEY BE TRANSMISSIBLE TOO?