CHAPTER 10

GERSTMANN-STRÄUSSLER-SCHEINKER DISEASE

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Abstract: Gerstmann-Sträussler-Scheinker (GSS) is a slowly progressive hereditary autosomal dominant disease (OMIM: 137440) and the first human transmissible spongiform encephalopathy (TSE) in which a mutation in a gene encoding for prion protein (PrP) was discovered. The first "H" family had been known by the Viennese neuropsychiatrists since the XXth century and was reported by Gerstmann, Sträussler and Scheinker in 1936. In this chapter we present the clinical, neuropathological and molecular data on GSS with the mutations in the PRNP gene: at codons 102, 105, 117, 131, 145, 187, 198, 202, 212, 217 and 232. In several families with GSS the responsible mutations are unknown.

INTRODUCTION

Gerstmann-Sträussler-Scheinker (GSS) is a slowly progressive hereditary autosomal dominant neurodegenerative disease of the Central Nervous System (CNS) (OMIM: 137440) and the first human transmissible spongiform encephalopathy (TSE) in which a mutation in a gene encoding for prion protein (PrP) was discovered. The true prevalence is difficult to estimate but numbers in a range of 1-10/100 000 000 are quoted.[1]

According to Budka et al,[2] GSS is defined as a neurodegenerative disease "in family with dominantly inherited progressive ataxia and/or dementia): encephalo(myelo)pathy with multicentric PrP plaques" (Figs. 1,2).

The first "H" family had been known by the Viennese neuropsychiatrists since the 20th century and was reported by Dimitz in 1913,[3] then by Gerstmann in 1928[4] and again by Gerstmann, Sträussler and Scheinker in 1936.[5] Later on Scheinker became an established neuropathologist and published, among other works, *Neuropathology in Its Clinicopathologic Aspects*.[6]

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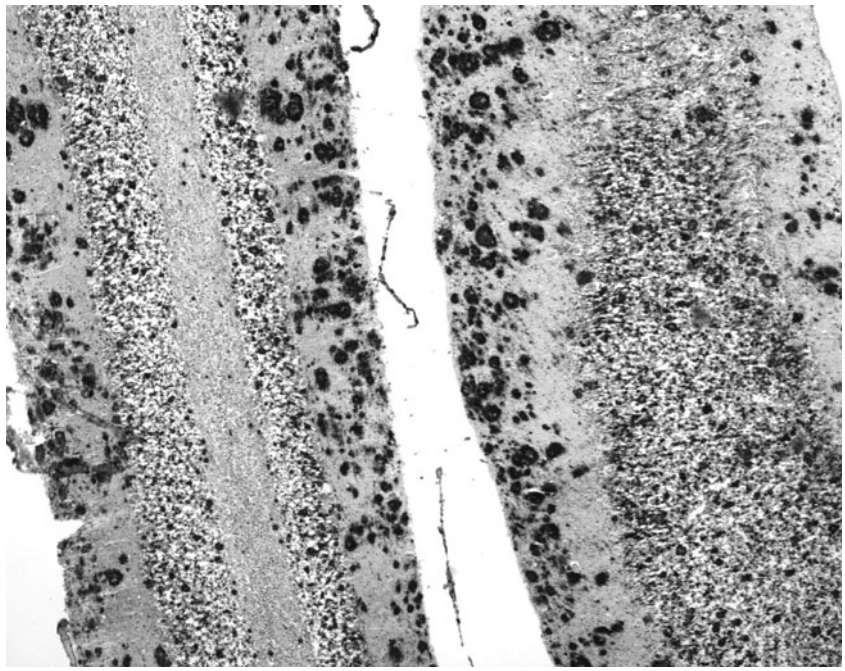

Figure 1. Cerebellum loaded with plaques from a case of the 232 mutation.[87]

Gerstmann in 1928 described a peculiar reflex, when a patient extended both arms in front of the chest and then the head was turned to one side, both arms crossed moving to the midline.[4] The arm contralateral to direction of turning was placed above the other arm. Subsequent members of the same family were described by von Braunmühl[7] and Franz Seitelberger, then director of the Obersteiner Institute, Vienna, Austria.[8,9] Seitelberger, four years before the discovery of the transmissible nature of kuru by Gajdusek et al[10] stressed the close neuropathological similarity (amyloid plaques—Figs. 1,2) of these two diseases and in a sense preconceived the transmissible nature of GSS.[11] The history of original GSS "H" family from Vienna is interesting. This family stems from a little rural town in the lower Austria (Niederoestereich) and had been diagnosed by local physicians as suffering from a form of hereditary neurosyphilis. As this diagnosis would stigmatize them, they decided to hide from doctors. In 1990, one of us consulted on a female case suspected of CJD whose father died with a diagnosis of "Friedreich ataxia". The maiden name of this case "H" was the name of the GSS family.[12,13] This discovery enabled modern studies of that fascinating kindred.

In 1981 a seminal paper by Masters et al[11] was published. In this paper, several GSS cases were proved transmissible to nonhuman primates. The Fujisaki strain of GSS (codon 102 mutation) first isolated by Tateishi et al[14] was passaged to mice, rats, guinea pigs and Squirrel monkeys. Another case with the same mutation[15] was passaged to Spider monkeys and to Marmosets.[16] To date, only inocula derived from 5 brains with 102^{Leu} could be transmitted.[17,18]

Of note, in the 1981 paper, Masters et al mentioned the "CG" family described by Worster-Drought et al.[19-21] While phenotypically similar to GSS in regard to amyloid plaques, this family had been later proved to represent Familial British Dementia with genetic alteration obviously different from that in GSS.[22]

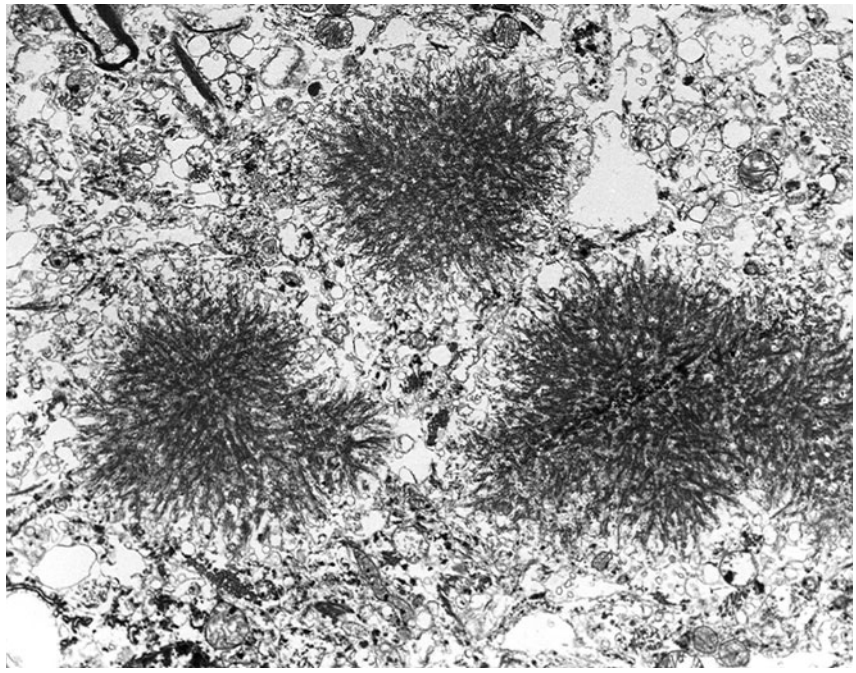

Figure 2. Electron microscopy of numerous plaques from a case of GSS from the "H" family.[12,13]

CODON 102 MUTATION (102^{Leu} 129^{Met})

GSS with mutation at codon 102 of the prion protein gene (*PRNP*) was the first target of molecular-genetic approach in 1989.[23] At codon 102, a mutation leading to a substitution of Pro (CCG) by Leu (CTG) was found. This mutation was subsequently found in several families from Japan including, "I" family;[24,25] Germany[26,27]—in the well characterized Sch. family,[28-31] Israel,[32] Hungary;[33] Poland,[34] UK,[35,36] Italy,[37-39] and in the original Viennese "H" family.[40]

The original family from which 4 cases were described by Seitelberger[9] numbered then 81 members; currently expanded to 221 member including 20 definitive GSS cases.[12] The disease manifests as slowly progressive cerebellar ataxia with dementia appearing late. The last case of GSS from this family (children of this female were tested for a mutation and proved negative for the codon 102 mutation) exhibited, however, features of otherwise typical CJD—i.e. early symptoms of dementia and a characteristic periodic EEG.

For some GSS families harboring the 102 codon mutation, a typical feature is heterogeneity of neurological signs and symptoms. The classical ataxic type starts in second to sixth decade and the duration of the disease ranges from a few months to a few years. Dysartria and alterations of saccadic eye movements, pyramidal and extrapyramidal signs and symptoms, cognitive changes leading to frank dementia are typical features. In a proportion of cases, a CJD-like disease type with myoclonic jerks and periodic EEG pattern is observed. MRI demonstrated mild atrophy of the cerebellum and the brain.

A separate problem is status of the codon 129 in a coupling with a mutated codon 102. In almost all GSS cases with this mutation, it is coupled with 129^{Met}. Cases coupled

with 129^{Val} are rare. A case described by Young et al[41] was a 33-year-old male, clinically significantly different from those of 129^{Met}, with seizures as a first sign, lower limb paraesthesias and bilateral deafness. Dementia was not observed. This male died at the age of 45, some 12 years after the first sings and symptoms were noticed.[42]

GSS with a mutation of codon 102 is transmissible to non human primates[11,17] as well as to rodents.[14] It seems that GSS cases with 102 mutations transmitted thus far.

Antibodies raised against different segments of prion protein (PrP) sequence help to elucidate the composition of peptides forming plaques.[43] Plaques were labeled with Abs raised against PrP 90-102 and, in much smaller proportion, with Abs raised against peptide PrP 58-71. Plaque cores were also strongly stained with Abs raised against residues 95-108, 127-147 and 151-165. Abs raised against PrP residues 23-40 (N-terminus) and 220-231 (C-terminus) stained peripheries of plaques as ring-shaped structures. Some plaque cores are labeled, however, with all Abs irrespective whether raised against either midportion of PrP or its N- and C-terimini. The latter findings indicate that both truncated peptides and full-length PrP may form amyloid fibrils but the truncated fibrils predominated.

MUTATION OF CODON 105 (105^{Leu} 129^{Val})

This mutation was found in 5 GSS families, all from Japan.[44-52] The disease manifests as spastic paraparesis with brisk reflexes and the presence of Babinski sign; in terminal stages, a patient becomes teraplegic, demented, with tremor and limb rigidity. Illness starts around 40-50 year of age and lasts 6-12 years. PrP deposits are encountered mainly in the cerebral cortex and less frequently in striatum. The cerebellum is affected only minimally. In two cases, sparse neurofibrillary tangles composed of paired helical filaments were seen.[44] Numerous neurofibrillary tangles [NFTs] were found in a case of 57-year-old female with dementia but not spastic paraparesis.[52] Of note, in a case described by Amano et al,[44] another type of plaques were seen—localized in the fifth and sixth layers of cerebral cortex, weakly PAS-positive, confluent and of laminar distribution.

MUTATION OF CODON 117 (117^{Val} 129^{Val})

This mutation was discovered in families characterized by dementia but not by otherwise typical for GSS cerebellar ataxia ("telencephalic type").[53-62] Mastrianni et al[58] described the cerebellar syndrome. In an Alsatian family, in earlier generations, only "pure" dementia was observed. In more recent generations, more complex pattern of signs and symptoms, including dementia, were noticed. Amyloid plaques were reactive with Abs raised against the central region of PrP while Abs to the C- and N-termini of the molecule stained the peripheries of plaques.[63] A 7 kDa peptide of PrP^{d} was found by Western blot,[63-65] but the presence of PrP^{d} varied; in some samples no PrP^{d} was found.[64,65] Also in the brain of an asymptomatic carrier, no PrP^{d} was seen.[64,65]

MUTATION OF CODON 131 (131^{Met} 129^{Val})

This mutation was found in only one family characterized by dementia, apraxia, cerebellar ataxia, extrapyramidal signs and brisk tendom reflexes.[66] The disease started in

the 5th decade and lasted for 9 years. MRI demonstrated cerebral and cerebellar atrophies. The family history was negative. Numerous PrP-amyloid plaques and diffuse deposits were seen in cerebral cortex, basal ganglia and cerebellum.

MUTATION OF CODON 145 (145^{Stop})

This mutation was discovered by Kitamoto et al[67] in a case with spastic paraparesis and progressive severe dementia. Neuropathological examination revealed numerous PrP plaques and PrP deposits in the wall of brain vessels as well as meningeal vessels (PrP-congophilic angiopathy). NFT were seen in the neocortex.

MUTATION OF CODON 187 (187^{Arg} 129^{Val})

This mutation was found in one American GSS family from the USA.[68] Nine affected cases were characterized by dementia, cerebellar ataxia, myoclonic jerks and seizures. The median age at onset is 42 years (range 33-50 years) and the duration of illness ranges from 8 to 19 years. Neuropathological examination revealed PrP^{d} deposits in cerebral cortex of distinct "curly" appearance and laminar pattern. PrP plaques were absent and spongiform change was not seen.

MUTATION OF CODON 198 (198^{Ser} 129^{Val})

This mutation was discovered in a family from Indiana ("Indiana kindred", IK)[69] and in another unrelated family.[70] Patients are homozygous or heterozygous in respect to Val at codon 129.

The IK is characterized by pyramidal and cerebellar signs, dementia, dysarthria and progressive clumsiness and difficulties of walking, prominent parkinsonian features, bradykinesia, cogwheel rigidity but no tremors, optokinetic nystagmus and sleep disturbances.[71,72] Alterations of saccadic eye movements[73] may be detected before other signs and symptoms appear. The disease starts between 40 and 70 years of age and in patients homozygous for $129^{Val\ Val}$ the beginning is approximately 10 years earlier than in heterozygous cases $129^{Val\ Met}$ patients. The disease lasts approximately 5 years (from 2 to 12 years) but may be accelerated to 1-2 years.

Neuropathological examination revealed changes otherwise typical for GSS.[74-82] Neurites around plaques contained NFT composed, not unlike those of Alzheimer's disease, of hyperphosphorylated MAP-τ. Spongiform change was occasionally visible around plaques.

Antibodies raised against different segments of PrP peptides helped to resolve the question of plaque composition.[43,83] Plaques are composed of two species of PrP—7 and 11 kDa spanning PrP residues 81-150 and 58-150 respectively. In contrast, nonfibrillar (pre-amyloid) PrP is immunolabeleld with antibodies raised against residues 23-40 and 220-231.[76] Abs raised against PrP residues 23-40 (N-terminus) and 220-231 (C-terminus) stained peripheries of plaques as ring-shaped structures.[84]

MUTATION OF CODON 202 (202^{Asn} 129^{Val}) AND MUTATION OF CODON 212 (212^{Pro} 129^{Met})[75,80,82]

The duration of illness of a case with 202^{Asn} was 6 years, the disease started in the 8th decade of life and manifested as dementia with cerebellar signs. PrP plaques were seen in both brain and the cerebellum. Numerous NFT were visible in the cerebral cortex. The patient with mutation 212^{Pro} became ill at the year 60 and the disease lasted for 8 years.[1] Slurred speech, cerebellar ataxia leading to total incapacitation but not dementia were seen. PrP plaques were visible in both brain and the cerebellum but their density was the lowest among all GSS families.

MUTATION OF CODON 217 (217^{Arg} 129^{Val})

This mutation was described by Karen Hsiao et al[56] in 2 patients from a Swedish-American family[74,76,85] with psychotic manic-depression disturbances, dementia, ataxia and parkinsonian features. The neuropathological picture is similar to that of IK; numerous PrP plaques and NFTs composed of paired helical filaments. PrP^{d} in plaques coexists with Aβ peptide.

MUTATION OF CODON 232 (232^{Thr})

This mutation was found by Liberski et al[86,87] in a case diagnosed earlier as olivo-ponto-cerebellar degeneration with spastic paraparesis and dementia. The disease started in the 5th decade of life and lasted for 6 years. Numerous PrP plaques were visible in the cerebral and cerebellar cortex and subcortical nuclei; in substantia, nigra Lewy bodies were seen occasionally.

UNKNOWN MUTATIONS

A few families (Italian-Canadian family;[88] "N" family[89]) and some others[90-94] were reported as GSS but the mutations were not known. The disease described by de Courten-Myers and Mandybur[95] was Alzheimer as later proved by immunohistochemistry.[96]

BIOLOGY OF GSS

Nomenclature

PrP^{Sc} is the pathological misfolded protein, insoluble in denaturing detergent; however, some pathological isoforms of PrP^{Sc} have recently been found not to be PK-resistant.[97] The neutral term "PrP^{d}" denotes the misfolded species of PrP which is disease-associated. PrP 27-30 is the proteolytic cleavage product of PrP^{Sc}.[98,99]

PrP PEPTIDES IN GSS

Two types of the unglycosylated isoforms of PrP^d may be present in human TSEs—Type 1 (21 kDa) and Type 2 (19 kDa). In GSS smaller peptides in the range of 7 to 8 kDa have been found. In GSS 102^{Leu}, two patterns of PrP^d were observed on the Western blot: a single 8 kDa band or 3 bands of 29, 27 and 21 kDa.[100] The 21 kDa peptide is N-truncated while the 8 kDa band is both N- and C-truncated. N-terminal sequencing revealed N-terminal cleavage site at residues 78, 80 and 82 for the 8 kDa peptide and residues 78 and 82 for the 21 kDa peptide. An additional cleavage site at residue 74 was found by mass spectroscopy for the 8 kDa peptide. It is interesting, that the 21 kDa PrP^d was purified only from those GSS brains where spongiform change was also seen.[100] A peptide of 7 kDa is associated with GSS 117^{Val}.[63] Microsequencing and mass spectroscopy revealed several N-terminal cleavage sites at residues 85-95. The most frequent were residues 88, 90 and 92 of PrP. The C-terminus was also ragged and ended with residues 148, 152 or 153. Of note, the 7 kDa peptide was derived only from the mutated allele.

CONCLUSION

In conclusion, GSS is a neurodegenerative diverse of diverse clinicopathological picture. The hallmark of microscopic picture is a multicentric plaque and thus, GSS is a prion disease similar to kuru.

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