PATHOPHYSIOLOGY OF *WDR45* MUTATION SENDA / BPAN IN AUTOPHAGY DISEASE

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Background

It is well known that autophagy is an essential biological mechanism for all organisms. Static encephalopathy of childhood with neurodegeneration in adulthood (SEDA) or beta propeller protein associated neurodegeneration (BPAN) is a disease caused by autophagy dysfunction. SENDA / BPAN is based on *WDR45* mutation at Xp11.23 and is a part of the novel neurodegeneration with brain iron accumulation (NBIA). Its pathophysiology is largely unknown.

Fig1. Disease classification of SENDA / BPAN

Fig2. Clinical course of SENDA / BPAN

Method

WIPI-4, LC3 the maker of autophagosome, and p62 the substrate of autophagy expression was analyzed by immunohistochemistry and qRT-PCR using RNA extracted from the substantia nigra (SN), globus pallidus (GP), thalamus (Th), frontal cortex (FC), and cerebellar cortex (CC) of post-mortem human brains obtained from SENDA/BPAN patient and three control patients.

Results

Case	Mutation	Initial walking	Speech ability	Epilepsy	Psychomotor regression
1	c.400C>T (p.Arg134*)	NA	No word	+	Static
2	c.400C>T (p.Arg134*)	NA	No word	+	Static
3	c.831-1G>C	NA	No word	+	Progressive
4	c.868C>T:p.Gln290*	NA	No word	+	Progressive
5	c.830+1G>A	1y 7m	No word	+	Progression from 1 to 4years, and stable
6	c.516G>C (p.Asp174Valfs*29)	2y 7m	One word	+	Progressive from teenage
7	c.519+1_519+3del	1y 6m	One word	+	Progressive
8	c.439+1G>T (p.[Gly147Val; Val147_Leu148ins8])	3y	No word	+	Progressive
9	c.1033_1034dup (p.Asn345Lysfs*67)	1y 6m	Few words	+	Progressive
10	c.322del (p.Ser108Leufs*10)	1y 3m	No word	+	Progressive from 28years
11	c.437dup (p.Leu148Alafs*3)	2y 2m	No word	+	Progressive
12	c.19C>T (p.Arg7*)	1y 6m	Three words	+	Progressive from 30years
13	c.830+2T>C	3y	One word	+	Progressive from 21years
14	c.637C>T (p.Gln213*)	1y 6m	Two-word sentences	-	Progressive
15	c.56-2A>G	2y 0m	Two-word sentences	+	Progressive from 38years
16	c.729-2A>G	NA	No word	+	Static

Table. Clinical characteristics

Fig3. WIPIs expression of SENDA / BPAN patient

WDR45 encodes the WIPI-4 protein which has three additional isoforms, WIPI-1, 2, and 3. WIPI-2 was the most dominant isoform, followed by WIPI-4 in most regions of SENDA/BPAN patient. Same tendencies were also indicated in the three control patients (data not shown).

Fig4. p62 expression of SENDA / BPAN and the three control patients
The p62 expression was high in the SN, GP and FC of SENDA patient compared to control patients. On the other hand, p62 expression was low in the CC of SENDA / BPAN patient compared to other control patients.

Fig5. Pathological features of the GP

LC3 was stained more strongly and neurospheroids were remarkable in the GP of SENDA patient. On the other hand, no LC3 staining and neurospheroids were seen in the GP of control patient. (×100, LC3 immunohistochemistry)

Discussion

- Why are severity and genotype not correlated with?
WDR45 is located on the X chromosome, hence subjects with X inactivation are predominantly affected.
- Why are MRI findings remarkable in the SN and GP ?
Although WIPI-4 expression is not vary in SENDA / BPAN and control patients, p62 is enhanced in the SN and the GP. Additionally, LC3 staining is enhanced in the GP. Under these conditions, autophagy must be impaired in the SN and GP and it leads to MRI findings .

Conclusion

The reason why the SN and GP experience severe accumulation of iron remains unclear because WIPI-4 is dominant in all regions. However, an increase of p62 expression and LC3 staining suggests an insufficiency of autophagy in the SN and GP.

Reference

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