Clinical Characteristics in Aged Patients with Rett Syndrome

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HIGHLIGHTS

Several characteristic features in aged RTT patients : bed-ridden state in 30-40s, atypical simplified hand stereotypies, well-controlled seizures, disappearance of aberrant breathing patterns and occasional appearance of obstructive sleep apnea, advanced dysphagia

Introduction :

The clinical features have not been investigated fully in aged patients with Rett syndrome (RTT), although it is speculated that the life prognosis is not so poor in RTT. We aimed to identify clinical characteristics in aged RTT patients, receiving long-term follow-up in our center.

Methods :

We retrospectively analyzed medical records in six patients with RTT, aged over 50, and having mutations in the gene of methyl-CpG-binding protein 2 (MECP2) (Figure 1).

Figure 1 : MECP2 mutaion of six patients

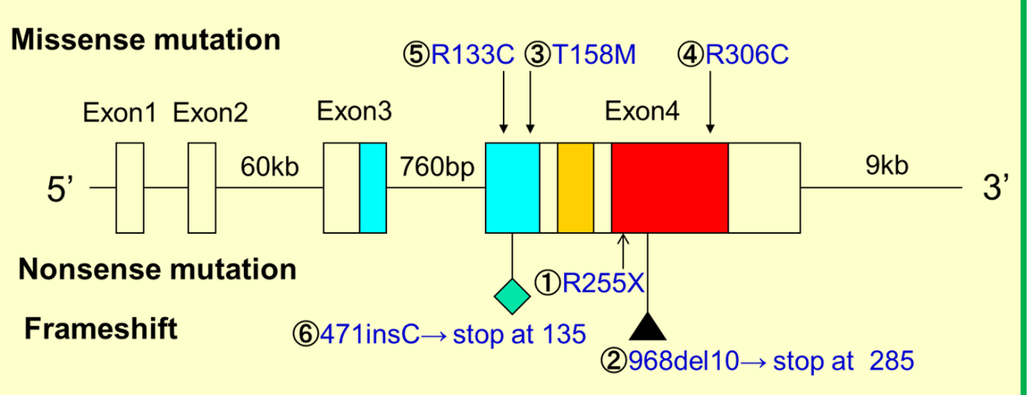

Table 1 : Profile and clinical data of six patients

1) Patient	1	2	3	4	5	6
Age , Sex	52y , F	53y , F	55y , F	54y , F	57y , F	54y , F
MECP2 mutation	R255X	285X	T158M	R306C	R133C	135X
Age on admission	6y	7y	7y	6y	11y	6y
OFC (at birth/on admission)	ND / −2.8SD	+0.1SD / +0.5SD	+0.1SD / −2.3SD	ND / −3.1SD	+0.1SD / <−3.0SD	ND / −1.9SD
2) Speech						
Acquired (age, level)	8m, single words	ND, single words	1y, single words	10m, single words	ND, single words	1y, babbles
Lost (age)	1y	3y	2y	3y	2y	ND
3) Gross mortor						
Head control	3m	3m	3m	4m	3m	3m
Rolling	2y	1y6m	6m	ND	7m	5m
Sit alone	7m	5m	7m	9m	7m	ND
Ambulation	1y6m, pull to stand	2y8m, walk alone	1y1m, walk alone 1y4m, run	1y, walk alone 1y4m, run	2y4m, walk alone	1y2m, walk with support
Age of regression	before 18m	before 18m	before 18m	before 18m	before 18m	2y
Clinical course	～30y, sit alone ～40y, sit withsupport 40y～, bedridden	～6y, sit alone, walk alone ～10y, walk with support ～38y, sit alone 38y～, bedridden (after left femoral fracture)	7～10y, lost walk, creep on the knees 10y, Achilles Tendor Lengthening 10～40y, acquired walk alone again ～50y, walk with support 50y～, sit with support	～11y, walk alone ～40y, sit alone 40y～, bedridden (after prolonged bed rest with the flu)	～4y, walk alone ～20y, little sit alone ～30y, sit with support 30y～, bedridden	～8y, pull to stand ～20y, sit alone ～35y, sit with support 35y～, bedridden
4) Hand stereotypies						
Lost hand use	1y3m	1y6m	2y	ND	ND	ND
Clinical course	6～10y, clasping one hand ～20y, wringing, clasping one hand scratching face/body	3～10y, wringing ～20y, wringing scratching face/body ～30y, scratching face/body	4～15y, wringing mouthing joined hands ～40y, wringing	3～6y, mouthing one hand ～30y, wringing mouthing one hand	3～10y, mouthing one hand ～20y, mouthing one hand clasping one hand, scratching face ～40y, mouthing one hand	3y～6y, wringing ～10y, clapping mouthing one hand, mouthing joined hands ～20y, mouthing one hand
Present	scratching face (left) no movement with rigidity (right)	scratching face/body (both)	scratching face (right) no movement with rigidity (left)	scratching head (right) no movement with rigidity (left)	scratching face/body (both)	little clasping (right) no movement with rigidity (left)
5) Epilepsy						
Sz onset	6y	5y	3y	3y	2y	5y
Clinical course	10～20y, monthly 24y～, Sz free	10～20y, daily 40y～, Sz free	10～20y, monthly, yearly 40y～, Sz free	10～20y, monthly 50y～, Sz free	2～7y, yearly 7y～, Sz free	5～7y, yearly (status epilepticus) ～24y, Sz free 24y～, daily, weekly 50y～, Sz free on LEV
Sz types	GTC, T, Myoclonus	GTC	GTC	GTC	GTC	GTC, T
AED	PHT, PB, CBZ → PB, CBZ	PHT, CBZ, PRM, ESM → PHT, PB, CBZ	PB	PHT, CBZ, NZP, PRM → PB, CBZ	PHT, CBZ → CBZ	VPA, PHT, PB, LEV → PB, LEV
Brain MRI	27y mild atrophy of cerebrum	41y lacunar infraction of left basal ganglia mild atrophy of cerebrum	33y mild atrophy of cerebrum	36y lacunar infraction of right basal ganglia	34y mild atrophy of cerebrum	47y atrophy of cerebrum / brainstem
6) Breathing disorders						
Severity	severe	severe	absent	mild	unclear	mild
Onset	9y	3y	–	5y	–	–
Clinical course	10～20y, frequent deep breathing, shallow breathing hyperventilation, breath hold	5～20y, frequent hyperventilation, breath hold ～40y, rare breath hold	–	5～40y, occasional breath hold	10～20y, monthly, arrest of breathing with cyanosis (Sz susp. at the time) 20～40y, weekly, unexpected dyspnea (BA susp. at the time)	–
Present	rare, breath hold 50y～, obstructive sleep apnea	mostly normal breathing 40y～, obstructive sleep apnea	–	mostly normal breathing 40y～, obstructive sleep apnea	40y～, stable after laryngotracheal separation	40y～, obstructive sleep apnea
7) Dysphagia						
Severity	severe	moderate	mild	mild	severe	severe
Clinical course	30y～, aspiration pneumonia ↑	40y～, poor swalloing aerophagia ileus	–	–	30y～, aspiration pneumonia ↑ 40y～, laryngotracheal separation poor gastric peristalsis	40y～, aspiration pneumonia ↑
Administration	40y～, tube feeding	40y～, tube feeding + oral feeding (once)	oral feeding (three times)	oral feeding (three times) + fluids, tube administration	40y～, tube feeding	40y～, tube feeding

F : female, y : years, m : months, OFC : occipitofrontal circumference, SD : standard deviation, ND : no data, Sz : seizure, GTC : generalized tonic clonic, T : tonic, AED : antiepileptic drug, PHT : phenytoin, PB : phenobarbital, CBZ : carbamazepine, PRM : primidone, ESM : ethosuximide, PRM : primidone, ESM : ethosuximide, NZP : nitrazepam, VPA : valproic acid, LEV : levetiracetam, BA : bronchial asthma

Results (Table 1) :

1) Five of six patients developed microcephaly.
2) All patients were not able to speech by the age of 3 years.
3) Four patients became to walk alone by the age of 3 years, whereas the other two patients only acquired pulling to stand or walking with support around the age of 2 years. Five patients became bedridden in their 30-40s.
4) Hand stereotypies showed reductions of frequencies with age, and the patterns of stereotypic movements became simplified and atypical.
5) All patients had epilepsies, and the first seizures occurred between the ages of 2 and 6 years. Remissions of seizures were achieved with treatments of 1-4 AEDs in all the patients. Seizure frequencies were decreased in their 20-30s.
6) Breathing disorders were seen in three of six patients, being less predominant with age, although four patients developed obstructive sleep apnea.
7) Dysphagia was noticed in six patients, and the severities were related to breathing disorders , frequent seizures, and early loss of motor functions.

Conclusions :

Several characteristic features were recognized in our aged patients with RTT, indicating the necessity of nationwide and/or global survey in a large number of patients.

"Conflict of Interest (COI) of the Principal Presenter :No potential COI to disclose"