



# HANS Syndrome

## from Clinical and Pathophysiological View Points

Human Papillomavirus Vaccine-associated  
Neuroimmunopathic Syndrome  
in Japan

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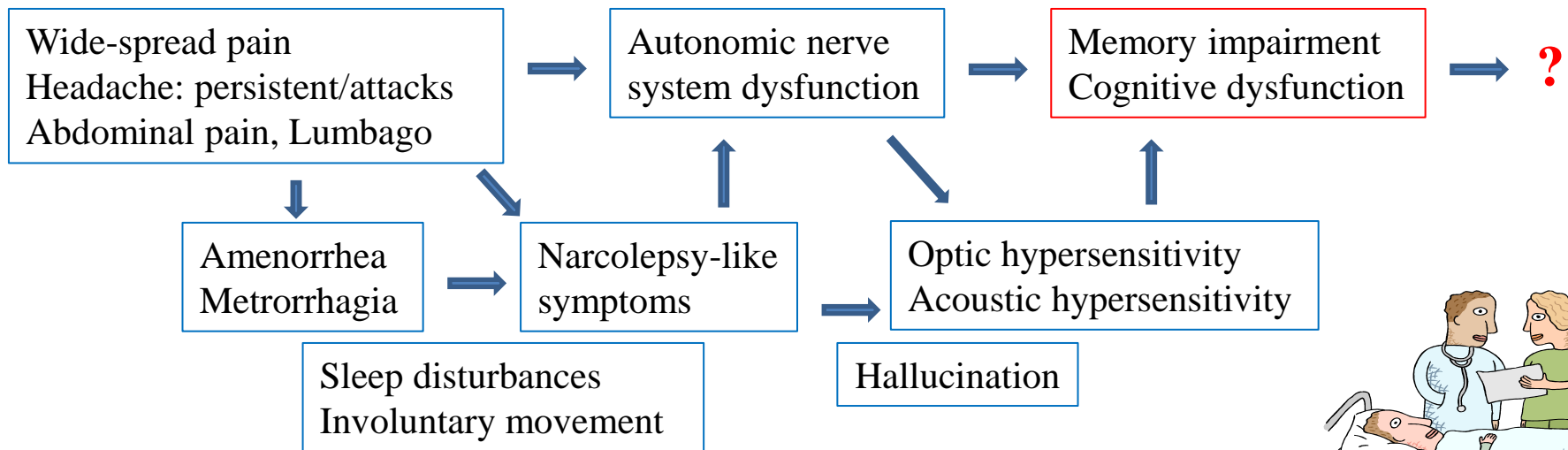
*Professor of Medicine, Institute of Medical Science, Tokyo Medical University*

*Trustee of Japan Medical Research Foundation*

# The First Encounter of HANS Patient in our Clinics

- The first patient (15 years of age, female) visited our Clinics in January, 2013.
  - HPV vaccines were administered 2 times, and she was getting ill just after the vaccinations.
  - She complained allodynia, fatigue, headache attacks, muscle weakness, numbness, hallucination, memory disorder, and cognitive dysfunction.
  - In the first, she was diagnosed as Juvenile Fibromyalgia and hospitalized to separate her from her environment for a while.
  - However, she was getting worse, and finally had wrist-cut.
- 
- Then, during the next half year 10 adolescents and young girls, who all received HVP vaccine, visited our Clinics with the similar complaints.

## ● Disease Course of this Patient (blood tests, CT, MRI, EEG = within normal limits)

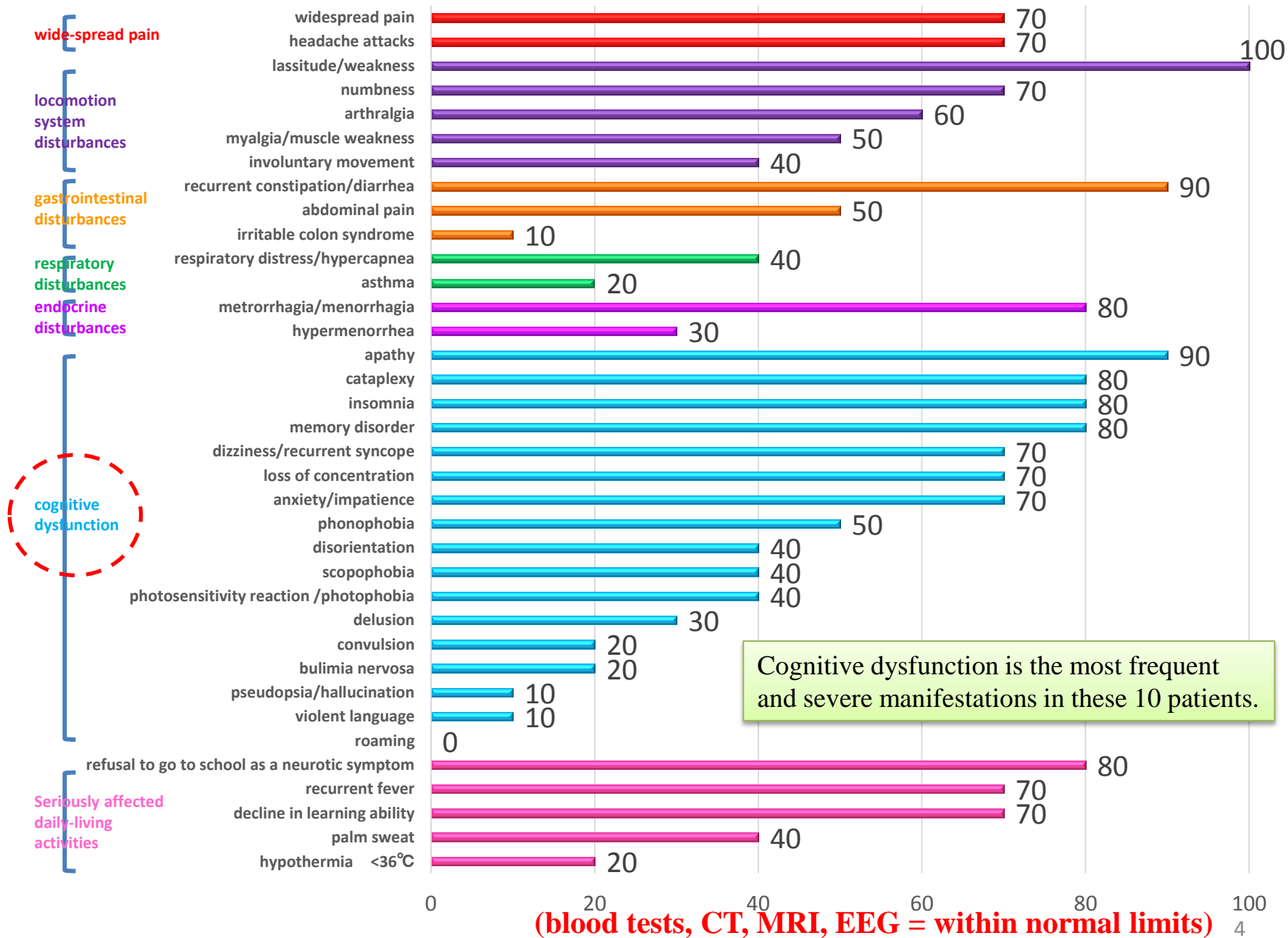


# HPV Vaccination and Onset of HANS: Symptoms and Signs

case No.	birth date	vaccine	1st vaccination → symptoms	2nd vaccination → symptoms	3rd vaccination → symptoms
	age at investigation				
1	18/Jan/2000	Cervarix	10/Oct/2012 → none	10/Oct/2012 → 5/Dec/2012 (8 w)	8/Mar/2013 → 12/Sep/2013 (24 w)
	14y 3m			①③②	①③④⑤⑥⑧⑩⑫⑭⑮⑯⑰⑱⑲⑳㉑㉒㉓㉔㉕㉖㉗㉘㉙㉚㉛㉜㉝㉞
2	28/Jan/1997	Cervarix	24/Aug/2011 → none	26/Sep/2011 → 8-10/Oct/2011 (2 w)	20/Feb/2012 → Apr-May/2012 (8-9 w)
	17y 3m			②③⑧	②③⑧⑯⑰⑱⑲⑳㉑㉒㉓㉔㉕㉖㉗㉘㉙㉚㉛㉜㉝㉞
3	19/Apr/1998	Cervarix	24/Aug/2011 → none	26/Sep/2011 → Jan/2012 (12 w)	20/Feb/2012 → Mar/2012 (2-3 w)
	16y 0m			⑯⑰⑱	②③⑧⑩⑯⑰⑱⑲⑳㉑㉒㉓㉔㉕㉖㉗㉘㉙㉚㉛㉜㉝㉞
4	15/Feb/1997	Cervarix	15/Aug/2011 → 15/Aug/2011	20/Sep/2011 → Nov/2011 (6 w)	16/Feb/2012 → gradually worsen
	17y 3m		⑰	①②③④⑦⑯⑲⑳㉑	①②③④⑤⑥⑩⑫⑬⑭⑮⑯⑰⑱⑲⑳㉑㉒㉓㉔㉕㉖㉗㉘㉙㉚㉛㉜㉝㉞
5	1/Jul/1997	Cervarix	8/Aug/2011 → none	10/Sep/2011 → none	3/Mar/2013 → Apr/2012 (7-8 w)
	16y 10m				①③④⑤⑥⑫⑬⑮⑯⑰⑱⑲⑳㉑㉒㉓㉔㉕㉖㉗㉘㉙㉚㉛㉜㉝㉞
6	23/Feb/1994	Cervarix	6/Oct/2011 → 10/Oct/2011	8/Nov/2011 → 15/Nov/2011 (1 w)	30/Mar/2012 → 8/Apr/2012 (1-2 w)
	2-y 2m		⑳	①⑧㉑	①②③④⑥⑦⑧⑬⑯⑰⑱⑲⑳㉑㉒㉓㉔㉕㉖㉗㉘㉙㉚㉛㉜㉝㉞
7	2/Oct/1998	Cervarix	27/Jul/2011 → 27/Jul/2011	17/Oct/2011 → 24-26/Oct/2011 (1 w)	26/Mar/2012 → Apr/2012 (3-4 w)
	16y 7m		①②⑧⑯⑲⑳㉑	③⑧⑲⑳㉑	①②③④⑤⑥⑦⑧⑩⑬⑭⑮⑯⑰⑱⑲⑳㉑㉒㉓㉔㉕㉖㉗㉘㉙㉚㉛㉜㉝㉞
8	1/Apr/1998	Gardasil	24/Jul/2012 → 19/Aug/2012	5/Dec/2012 → 8/Jan/2013 (3 w)	none
	16y 1m		①③⑥⑯⑳㉑	①②③⑥⑦⑩⑪⑫⑬⑭⑮⑯⑰⑱⑲⑳㉑㉒㉓㉔㉕㉖㉗㉘㉙㉚㉛㉜㉝㉞	
9	20/Jul/1997	Cervarix	3/Sep/2011 → gradually progressed	6/Oct/2011 → gradually progressed	8/Mar/2012 → gradually progressed
	16y 9m		④	④	④⑥⑯⑰
10	12/Feb/1998	Cervarix	11/Sep/2010 → 12/Sep/2010	23/Oct/2010 → Feb/2011	28/Mar/2011 → a few days (1 w)
	16y 3m		⑰	②⑰	①③④⑥⑦⑧⑨⑩⑰⑲⑳㉑㉒㉓㉔㉕㉖㉗㉘㉙㉚㉛㉜㉝㉞

- |                         |                           |                           |                                     |                              |                         |                  |
|-------------------------|---------------------------|---------------------------|-------------------------------------|------------------------------|-------------------------|------------------|
| ① widespread pain       | ② headache                | ③ cataplexy               | ④ arthralgia/arthritis              | ⑤ involuntary limb movements | ⑥ myalgia/lassitude     | ⑦ tender points  |
| ⑧ constipation/diarrhea | ⑨ irritable colon disease | ⑩ anxiety                 | ⑪ visual and auditory hallucination | ⑫ acoustic hyperesthesia     | ⑬ optic hyperesthesia   | ⑭ palm sweat     |
| ⑮ scopophobia           | ⑯ menstrual irregularity  | ⑰ lumbago                 | ⑱ absence of school                 | ⑲ numbness of extremities    | ⑳ persistent mild fever | ㉑ fever (>38 °C) |
| ㉒ concentration drop    | ㉓ memory disorder         | ㉔ orientation disturbance | ㉕ dizziness/syncope                 | ㉖ hypersomnia                | ㉗ sudden sleep attack   | ㉘ delusion       |
| ㉙ decreased scholarship |                           |                           |                                     |                              |                         | 3                |

# Clinical Symptoms & Signs of 10 Patients with Adverse Events after HPV vaccination



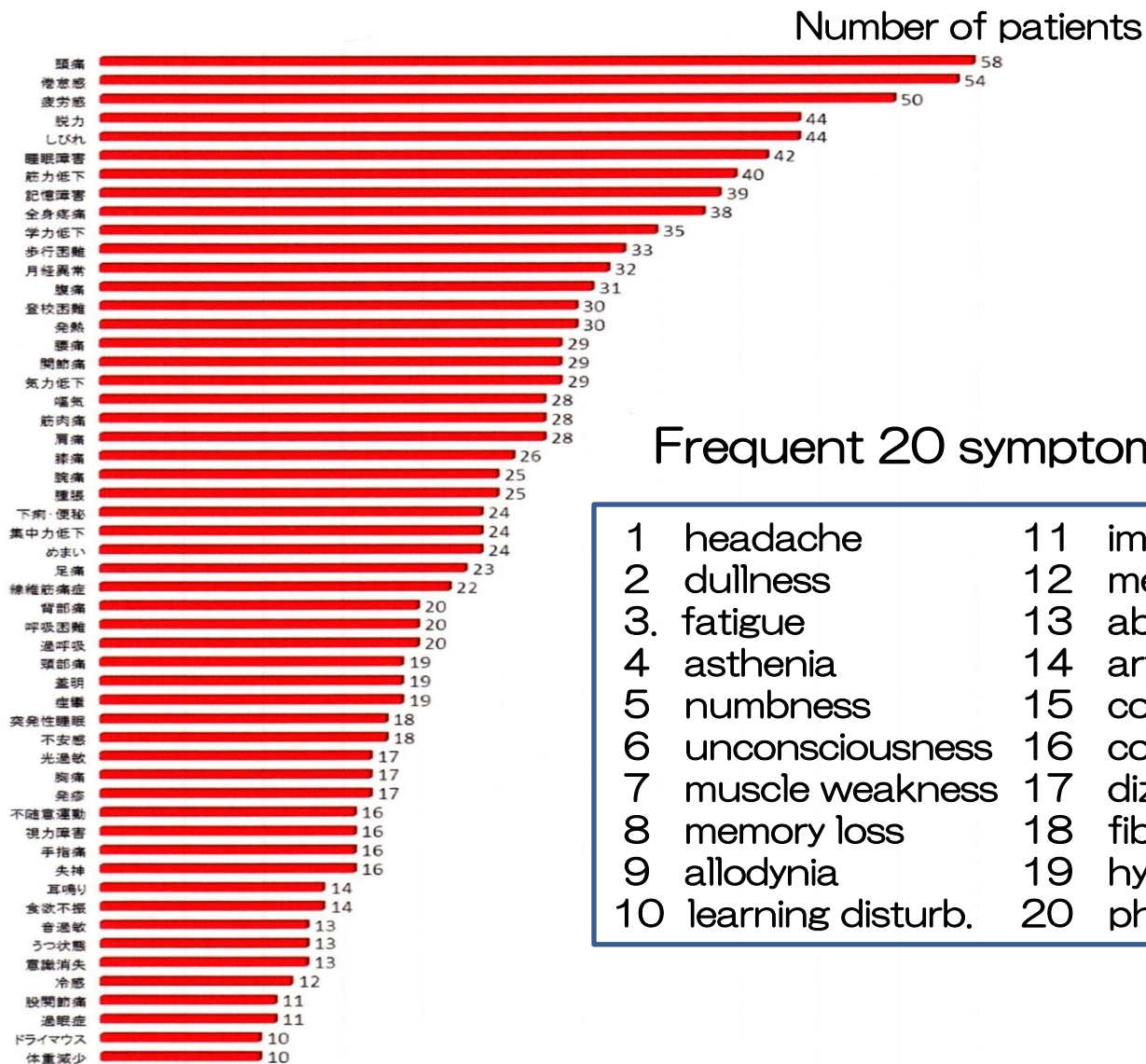
# Adverse Events after HPV vaccination

reported by *the Ministry of Health, Welfare, and Labor* of Japan

Number of people received vaccination	~ 3,380,000 (MHWL)
Number of cases with adverse events reported	2,475 (0.074%)
Number of cases with serious adverse events	1,231
Clinical symptoms reported	7,676
Serious clinical symptoms	4,649

# Clinical Symptoms & Signs of 88 Patients with HANS

Symptoms & signs

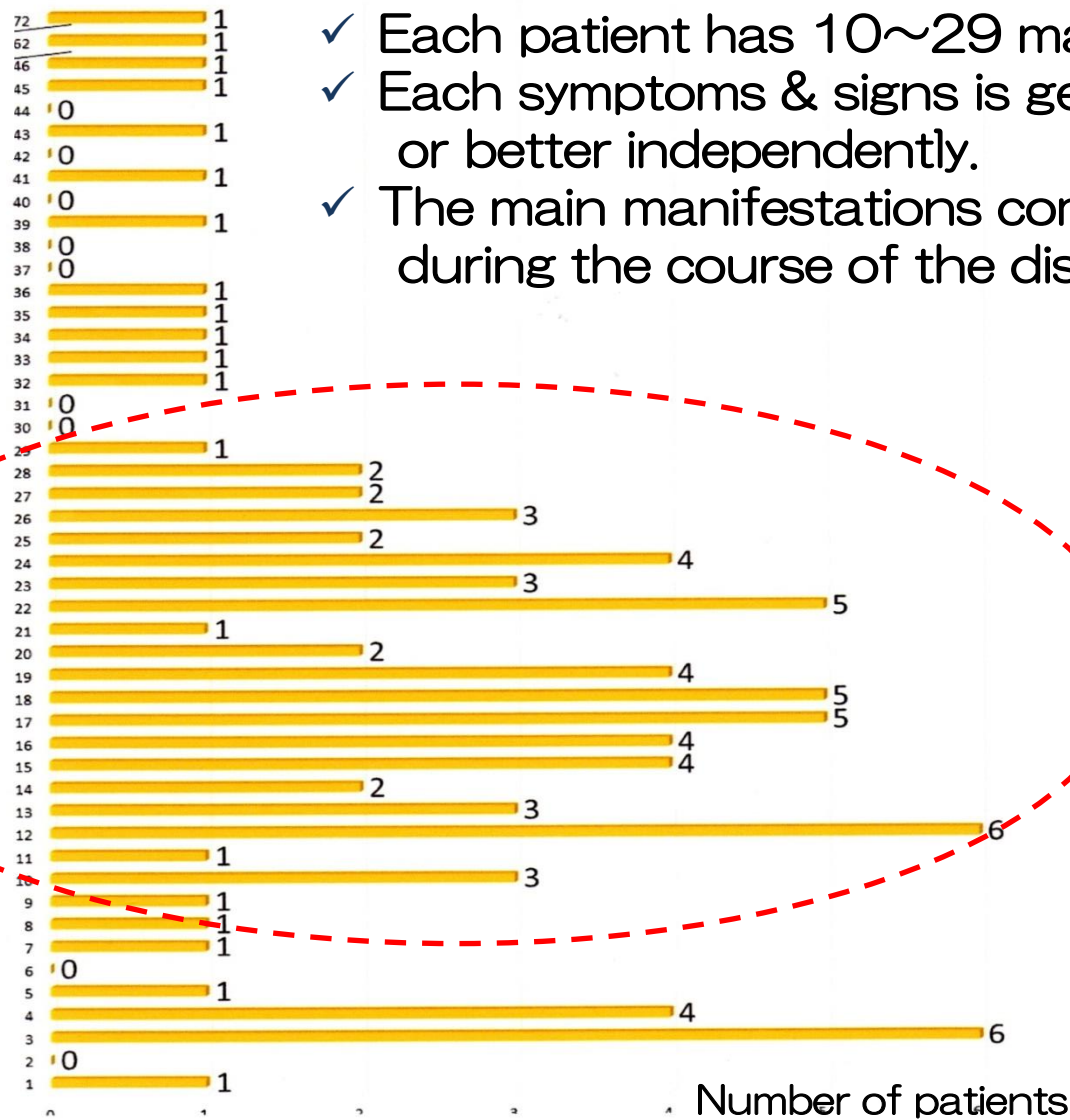


## Frequent 20 symptoms & sign

- |    |                   |    |                  |
|----|-------------------|----|------------------|
| 1  | headache          | 11 | impaired waling  |
| 2  | dullness          | 12 | menstral abnorm. |
| 3  | fatigue           | 13 | abdominal pain   |
| 4  | asthenia          | 14 | arthralgia       |
| 5  | numbness          | 15 | constipation     |
| 6  | unconsciousness   | 16 | concentr. drop   |
| 7  | muscle weakness   | 17 | dizziness        |
| 8  | memory loss       | 18 | fibromyalgia     |
| 9  | allodynia         | 19 | hyperventilation |
| 10 | learning disturb. | 20 | photosensitivity |

# Number of Symptoms & Signs of 88 Patients with HANS

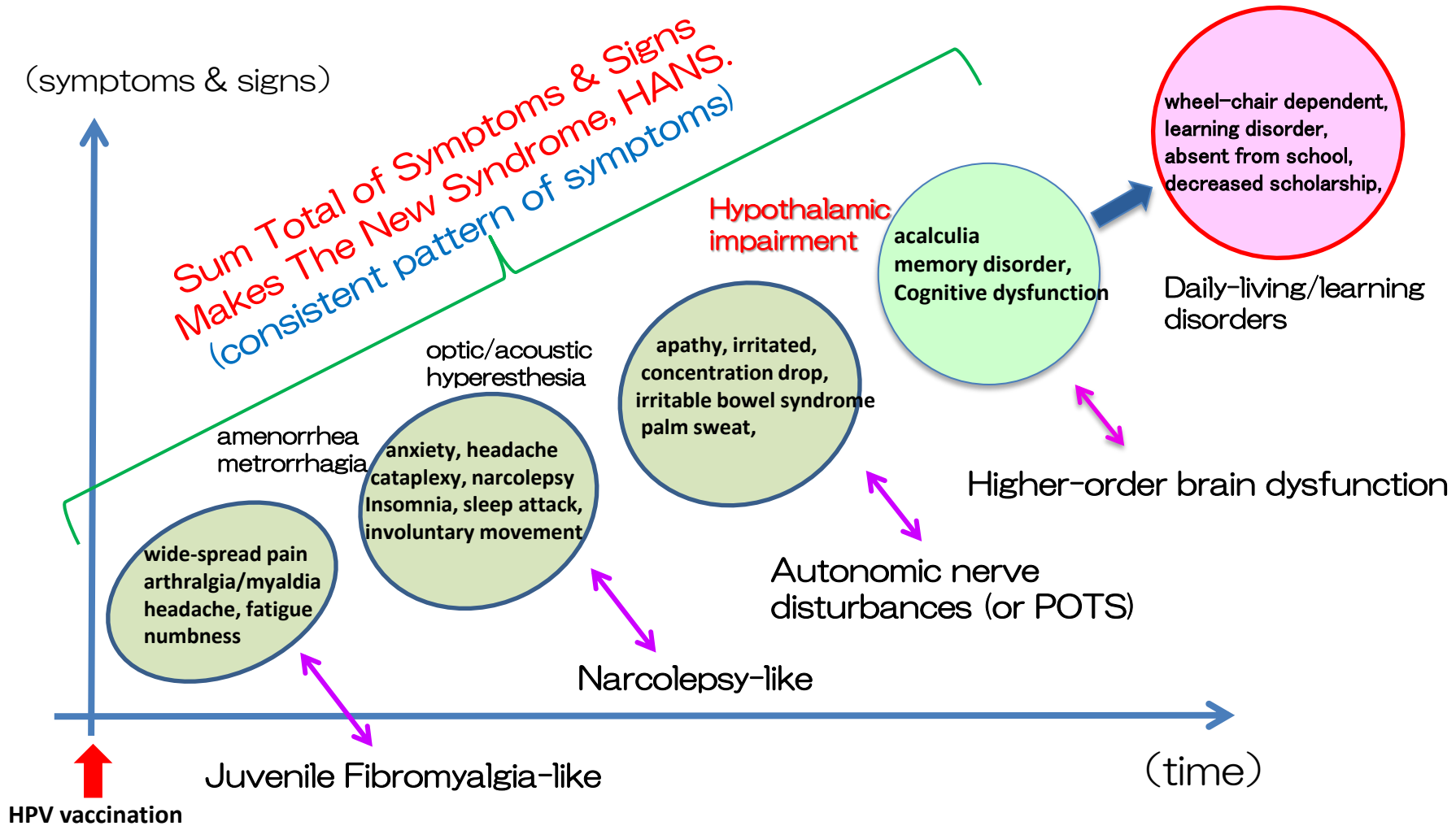
Number of Symptoms & Signs



- ✓ Each patient has 10~29 manifestations.
- ✓ Each symptoms & signs is getting worse or better independently.
- ✓ The main manifestations come and go during the course of the disease.

# Progression of Symptoms & Signs in Disease Course

A New Syndrome : HPV-associated Neuroimmunopathic Syndrome (HANS)



(blood tests, CT, MRI, EEG = within normal limits)



# Common and Specific Manifestations

## □ Common symptoms & signs

allodynia, headache, dullness • fatigue, numbness, dizziness, involuntary movement, sleep disturbances, abnormal menstration, photosensitivity, hyperacusis, Concentration drop, memory loss, cognitive dysfunction



autonomic nerve system dysfunction ?  
limbic system dysfunction ?  
central endocrine system dysfunction ?

## □ Rare but specific symptoms & signs

• diabetes insipidus	vasopressin
• menstrual abnormality	GnRH → LH-FSH
• osteoporosis/hypothalamus obesity	GRH → GH
• lactation/attachment	PRL/oxytocin



Hypothalamus-Hypophysis dysfunction ?

• restless leg syndrome	? dopamine ↓
• hallucination	? dopamine ↑
• multiple personality disorder	? attachment

## Symptoms due to Locomotor, Sensory and Autonomic Nervous System Disorders, and Cognitive Dysfunction

### Symptoms & Signs of HANS



### Systems disordered

1	orthostatic disorders, gait ataxia, convulsion involuntary movement.	Locomotor system disorders
2	wide-spread pain, optic/acoustic hyperesthesia, severe menstrual cramps.	Sensory system disorders
3	irritable colon syndrome, abdominal pain, hyperhidrosis, hyperventilation, thermoregulation disorder, circadian rhythm disorders (insomnia, hypersomnia), orthostatic syncope, menstrual irregularity, diabetes insipidus.	Autonomic nerve and endocrine system disorders
4	apathy, fatigue, anxiety, concentration drop, headache, narcolepsy, optic/acoustic hyperesthesia, panic disorder, acalculia, memory disturbances, countenance cognitive dysfunction, learning disturbances, memory impairment.	Cognitive dysfunction and emotional disorders

# Symptomatological Analysis

## Responsible Locus in CNS of HANS

	Cerebral cortex	Basal ganglia	Thalamus	Limbic system	Brain stem	cerebellum	Hypo-thalamus	Hypo-physis
Locomotor system symptoms	++	++	+	-	++	++	++	-
Somatosensory system symptoms	+	+	++	+	+	-	+	-
Optic/auditory/gustation system symptoms	+	-	+	+	+	-	+	+
Allergic symptoms	-	-	-	-	-	-	+	-
Autonomic nerve system symptoms	+	-	+	-	++	-	++	-
Endocrine system symptoms	-	-	-	-	-	-	++	++
Emotional/cognitive symptoms	++	+	+	++	+	+	++	+

# Symptomatological Analysis

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	Cerebral cortex	Basal ganglia	Thalamus	Limbic system	Brain stem	cerebellum	Hypo-thalamus	Hypo-physis
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Somatosensory system symptoms	+	+	++	+	+	-	+	-
Optic/auditory/gustation system symptoms	+	-	+	+	+	-	+	+
Allergic symptoms	-	-	-	-	-	-	+	-
Autonomic nerve system symptoms	+	-	+	-	++	-	++	-
Endocrine system symptoms	-	-	-	-	-	-	++	++
Emotional/cognitive symptoms	++	+	+	++	+	+	++	+

The primary central locus of HANS will be the hypothalamus-hypophysis axis.

# We proposed a new clinical disease entity ; the HPV-associated neuroimmunopathic syndrome ( HANS )

- Sum total of these symptoms and signs is a collection of them, and has a unique consistent pattern that does not readily fit into an existing diagnostic entity.
- The same set of manifestations was seen in different patients.
- They have been completely in normal physical condition and neuropsychiatric status before HPV vaccination. Their disorders were started just after the HPV vaccination.
- The complex of of these symptoms and signs were manifested in young females, but not in males no males.
- The age of patients were mostly between 14 ~ 19 years of age, and rarely below 13 and over 20. Thus, they belong to HPV vaccine-recommended age group.

⇒ HANS is a new disease entity occurred following HPV vaccination.

## Question 1

CRPS or POTS is merely a psychosomatic functional disorder, and thus exercising will be the best way of treatment alternatives !



# HANS is a complex syndrome, but not CRPS or POTS

- CRPS: Complex Regional Pain Syndrome. menstrual abnormalities (-)
- POTS: Postural Orthostatic Tachycardia Syndrome: allodynia (-)
  - ➔ memory disorders / cognitive dysfunction (-)

## *H A N S*

1	orthostatic disorders, gait ataxia, convulsion involuntary movement.	Locomotor system disorders
2	wide-spread pain, optic/acoustic hyperesthesia, severe menstrual cramps.	Sensory system disorders
3	irritable colon syndrome, abdominal pain, hyperhidrosis, hyperventilation, thermoregulation disorder, circadian rhythm disorders (insomnia, hypersomnia), orthostatic syncope, menstrual irregularity, diabetes insipidus.	Autonomic nerve and endocrine system disorders
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## Question 2

Why are the severe adverse events of HPV vaccine reported solely from Japan but not from other foreign countries?





# Frequency of Adverse Events in Denmark and UK

	Denmark	UK	Japan
No. of Vaccination	1,635,768	7,632,759	8,898,150
No. of People Vaccinated	630,000	2,670,000	3,380,000
No. of Patients with AE	1,730	8,243	(reported cases: 2,600)
No. AE	11,529	19,359	
AD Patients/1,000 vaccinated	2.7	3.1	<b>Suspected No. of Patients 9,126 ~ 10,478/3,380,000</b>

DK: [DHMA](#), Drug Analysis Print : Data lock 2015/7/31

UK: [MHRA](#), Case Series Drug Analysis Print : Data lock 2015/6/5

JP: [PMDA](#) AE Data Base : Data lock 2015/4/30

# AEs Reported from DM, FR, and UK

DHMA / ANSM / MHRA

SOC	Denmark	No.	%	France	No.	%	UK	No.	%
1	Neurological	1,778	28.3	Neurological	443	21.2	Neurological	4,263	29.8
2	General/Systemic	1,039	16.5	General/Systemic	400	19.1	General/Systemic	2,940	20.6
3	Bone-Joint/Muscle	671	10.7	Bone-Joint/Muscle	272	13.0	GI tract	2,100	14.7
4	Skin/Subcutaneous	645	10.3	Skin/Subcutaneous	645	9.1	Bone-Joint/Muscle	1,455	10.2
5	GI tract	539	8.6	Reproductive/Lactation	173	8.3	Skin/Subcutaneous	645	9.1
6	精神障害	238	3.8	感染症・寄生虫症	108	5.2	血管障害	436	3.1
7	眼障害	209	3.3	血液・リンパ系障害	100	4.8	呼吸器・胸郭・縦隔障害	370	2.6
8	呼吸器・胸郭・縦隔障害	176	2.8	胃腸障害	94	4.5	眼障害	281	2.0
9	心臓障害	119	1.9	免疫系障害	60	2.9	精神障害	232	1.6
10	感染症・寄生虫症	119	1.9	呼吸器・胸郭・縦隔障害	42	2.0	臨床検査	185	1.3
1~10 計		5,533	88.1		1,883	90.1		13,583	95.0
総計		6,279	100		2,092	100		14,300	100

2006/2/7~2015/2/26

総接種回数 1,592,694 回

報告総人数 1,331 例

副反応総件数 6,279 件

2006/11/23~2013/9/20

総接種回数 回

報告総人数 例

副反応総件数 2,092 件

2008/9/1~2012/7/31

総接種回数 約600万回

報告総人数 6,213 例

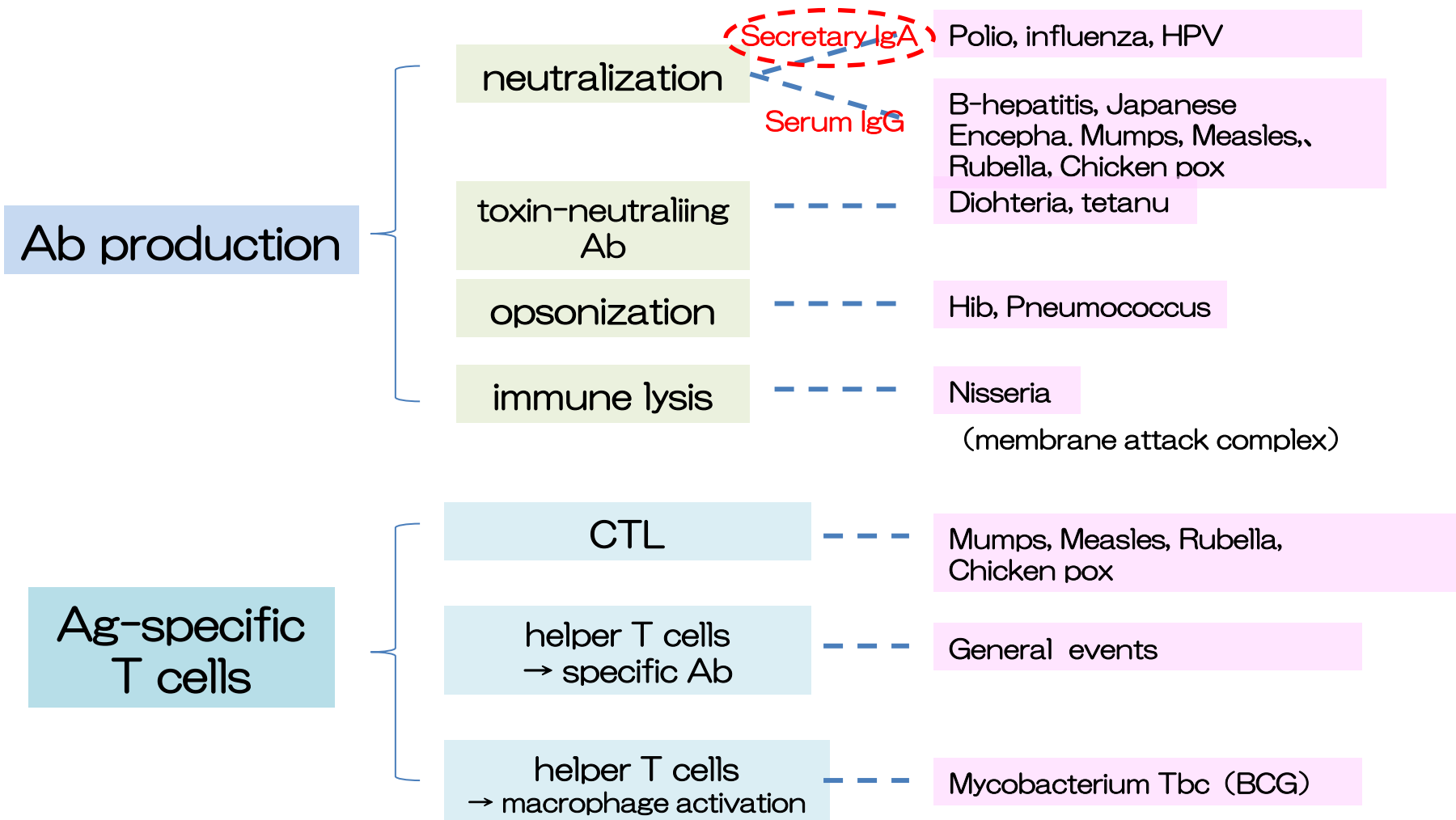
副反応総件数 14,300 件

## Question 3

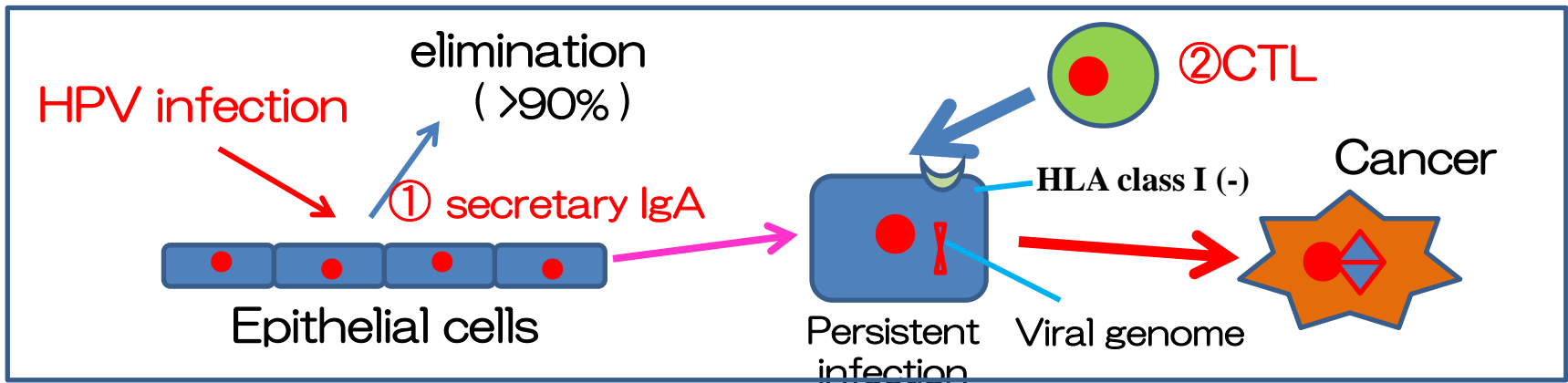
In case that HPV vaccination is suspended, many Japanese women will die due to cervical cancer in the next 10 years !



# Immunological Aspects of Vaccination Effects



# Protection from Viral Invasion Polio, Influenza, and HPV

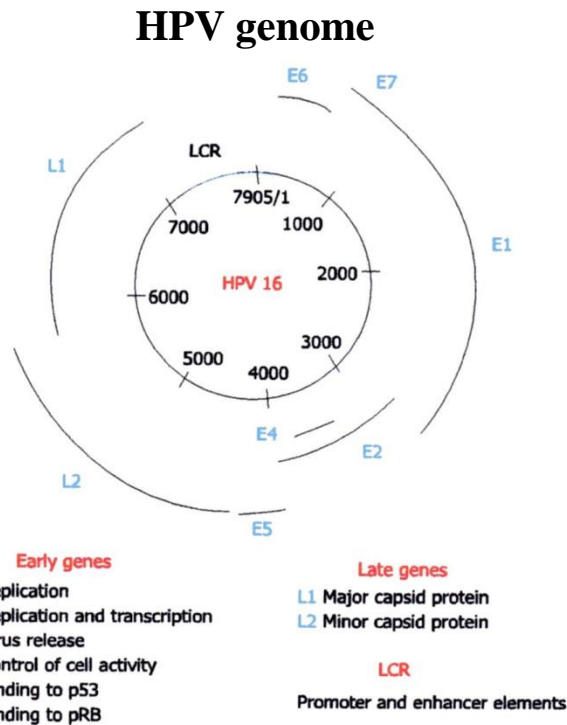


In cases of **polio virus** and **influenza virus**, serum IgG is effective for viremia which means that IgG blocks viruses invading into blood stream and reaching to CNS.

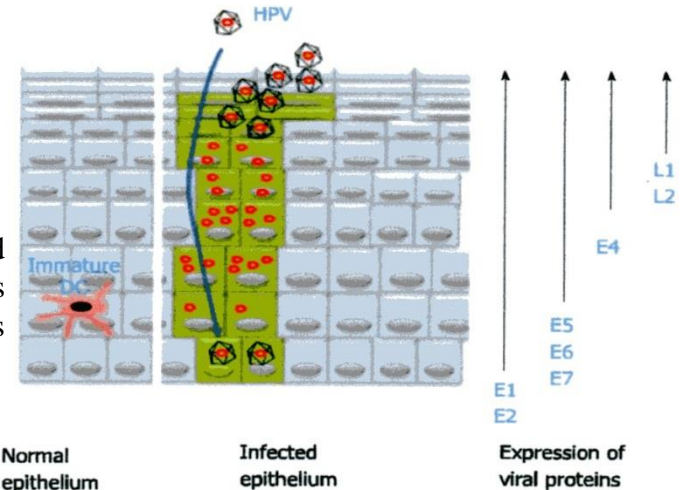
In order to produce secretory IgA, mucosal immune vaccine is developing in Japan ! Which means no more needs of Cervarix® or Gardasil.

# Immune Therapy for Human Papillomaviruses-related Cancers

(World Clinical Oncology, 2014;5:1002-19)

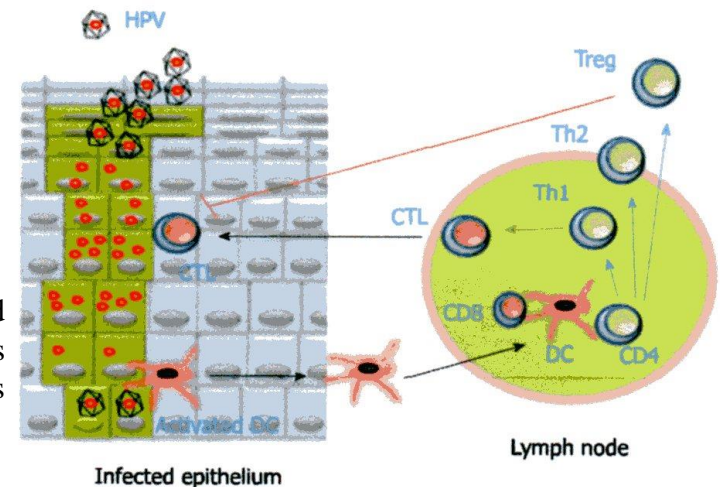


Non-keratinised stratified squamous epithelial lining cells



**Papillomavirus replication is tissue specific.**

Non-keratinised stratified squamous epithelial lining cells

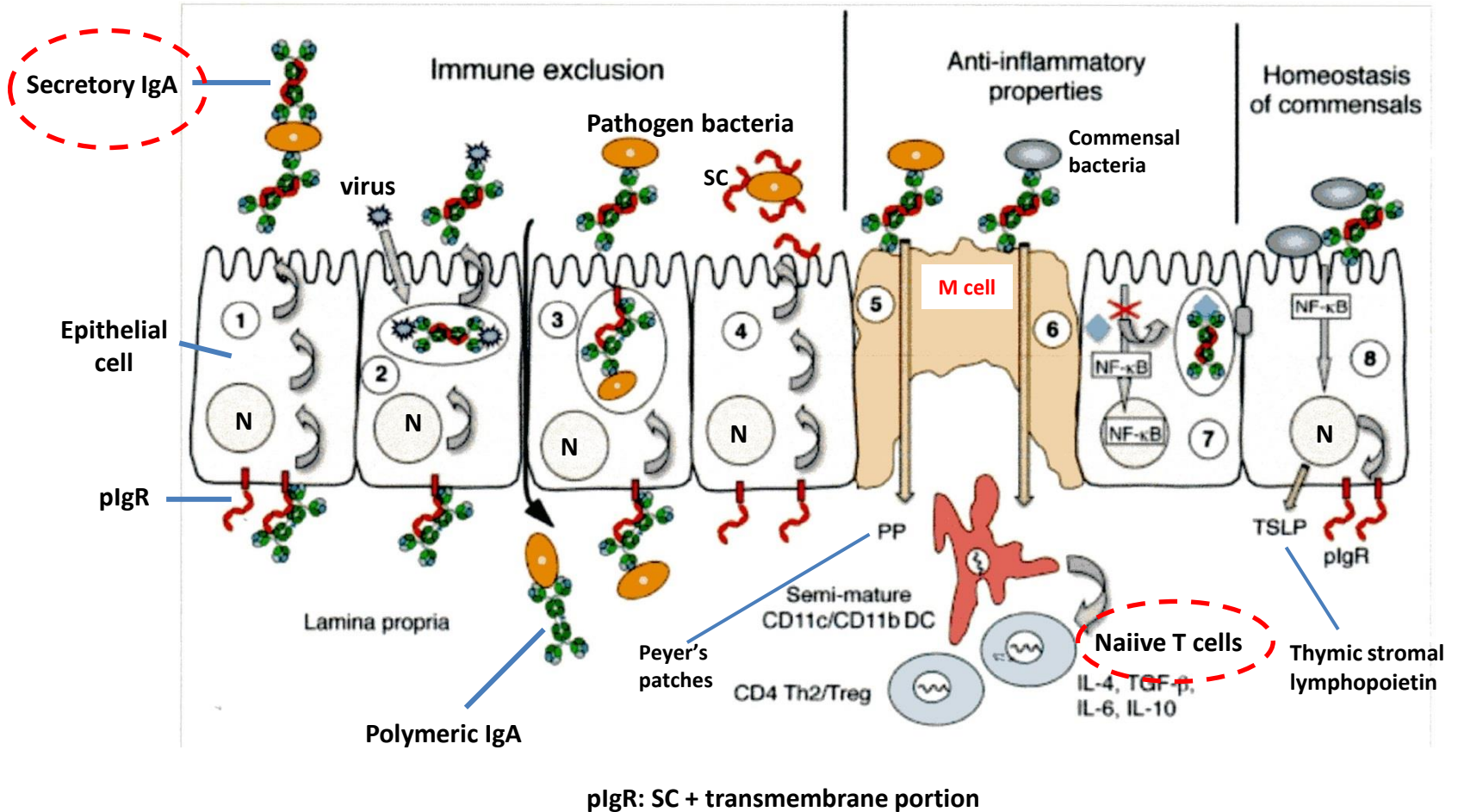


**Cellular immune response against HPV.**

# Noble HPV vaccine development strategies for inducing mucosal immunity

東大産婦人科川名准教授のグループ

「乳酸菌を利用したHPVワクチンの創製」：乳酸菌膜にE7-VLPを結合し、ソフト・カプセルに充填して内服する。

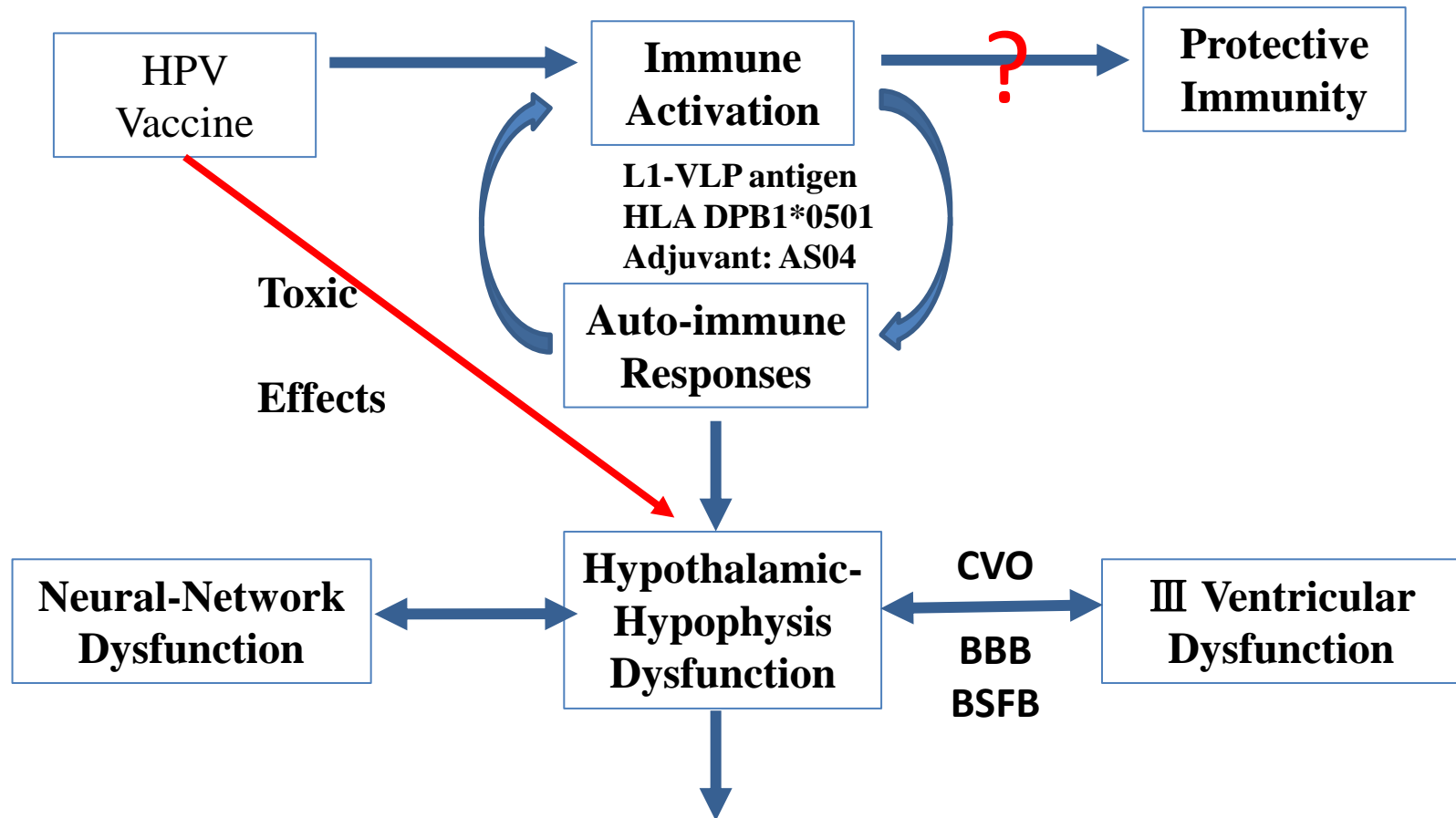


# Pathogenic Mechanisms





# Pathogenic Mechanisms of HANS



*Subacute Autonomic, Endocrine, and Cognitive Disorders (Kuroiwa)*

# Treatment of “HANS”



# Possible Approach to “Treatment”

## ● Anti-inflammatory Tx.

Methyl-prednisolone Pulse Therapy

Plasmapheresis / Absorption

Immunosuppressive agents

Prednisolone

Cyclophosphamide / MMF



Cytokines, Cytokine-R  
Inhibitors

## ● Symptomatic Tx.

Bronchodilator  
(phosphodiesterase inhibitor)

**Theophylline**

Anti-depressants

Paroxetine

Duloxetine

Anti-convulsants

Pregabalin

Lamotrigine

**Topiramate**

Dementia therapeutic agents

**Memantine**

\* The final prognosis of HANS is not known at this time.



**Thank you for your attention**