Beneficial Effects of Herbal Medicine on Susceptibility to Infection in a Patient with Immunoglobulin Deficiency

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Abstract: A case of immunoglobulin deficiency suffered from recurrent enterocolitis and otitis media was treated by Shoukenchuto, one of the Japanese herbal medicines (Kampo), and his susceptibility to infection markedly improved. The increase in the T cell percentage and in the lymphocyte proliferation in our patient suggests the importance of regulatory function of T cells for clinical improvement. The findings in our case and the previously reported cases suggest the usefulness of Japanese herbal medicine or Chinese medicine as an alternative or a supportive therapy for patients with immunological abnormalities.

Keywords: Herbal medicine, Shoukenchuto, immunoglobulin deficiency, CD4, CD8, lymphocyte proliferation.

We present a case of immunoglobulin deficiency with recurrent enterocolitis and otitis media whose clinical symptoms improved after treatment with Japanese herbal medicine (Kampo).

CASE REPORT

A 6-year-old boy developed complex partial seizures and EEG showed sporadic spikes in the central and parietal lobes. He was diagnosed as having partial epilepsy. Initially, valproate was administered, but carbamazepine was required for control of his seizures. After one year of medication with carbamazepine, he frequently suffered from enterocolitis or otitis media requiring many hospital visits almost every weeks and four times of hospital admission during the 2 years. Everytime, he required to be treated with continuous drip infusion and antibiotics repeatedly (Fig. **1**). His laboratory tests showed

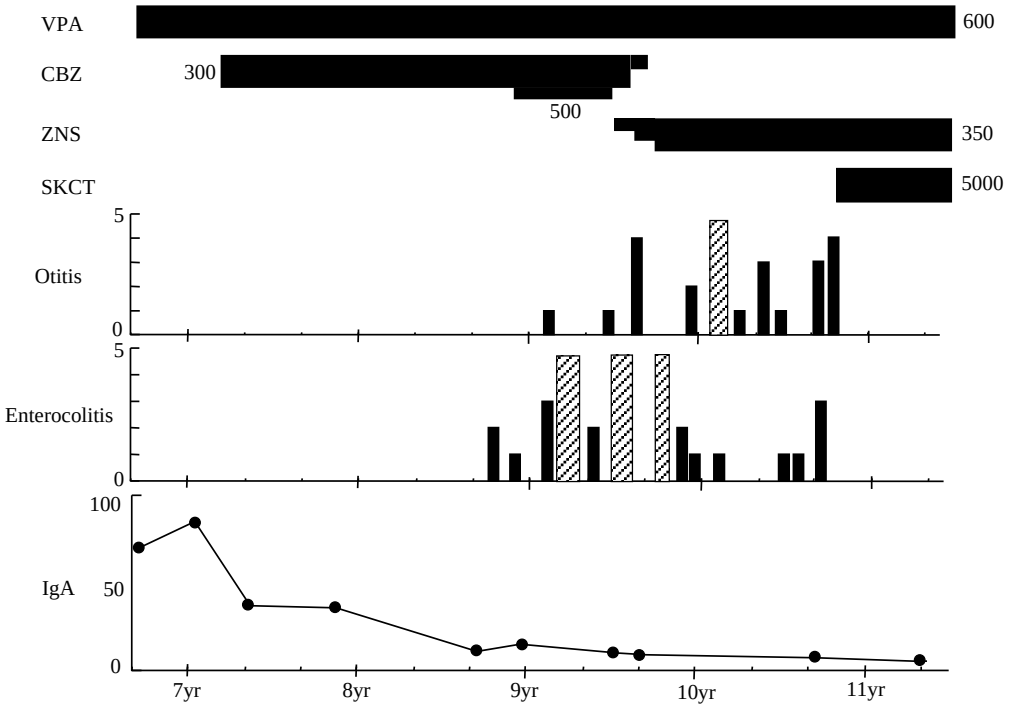

Fig. (1). Clinical changes in the patient. (Top) History of medication. VPA: valproate, CBZ: carbamazepine, ZNS: zonisamide, SKCT: Shouken-chu-to. The numbers indicate the dosages (mg/day). (Second and Third) Black bars indicate the number of hospital visits due to otitis or enterocolitis (visits/month). Shaded boxes indicate the period of admission. (Bottom) Serum IgA levels (mg/dl).

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Table1. Immunological Evaluation of the Patient

Age	Drug Dosage (mg/day)				Immunoglobulin (mg/dl)							B Cell Count (%)				Cell Surface Marker					Lymphocyte Proliferation (Stimulation Index)		
	VPA	CBZ	ZNS	SKCT	IgG	IgA	IgM	IgG1	IgG2	IgG3	IgG4	IgG+	IgA+	IgM+	IgD+	CD19	CD3	CD4	CD8	CD4/CD8	PHA	ConA	PWM
6yr 8m	600	0	0	0	788	70	282	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7yr 0m	600	0	0	0	883	85	285	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7yr 4m	600	300	0	0	765	37	185	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8yr 0m	600	300	0	0	587	36	124	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8yr 10m	600	300	0	0	617	11	133	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9yr 1m	600	500	0	0	693	15	172	634	o	23	<0.45	0	0	15	14	-	-	-	-	-	-	-	-
9yr 8m	600	200	50	0	584	10	99	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9yr 10m	600	0	350	0	616	9	89	367	9.5	24	<3.0	-	-	-	-	22.9	63.0	28.4	36.6	0.8	121.2	91.0	17.8
10yr 10m	600	0	350	0	680	7	92	443	<8.0	38	<3.0	1	0	11	11	-	-	-	-	-	-	-	-
11yr 4m	600	0	350	5000	849	5	115	471	<8.0	38	<3.0	1	1	14	13	15.1	68.7	36.0	42.0	0.9	220.9	199.7	47.7
Normal Ranges					(6yr) 630-1490	45-258	72-305	(8-10yr) 390-1235	61-430	10-98	1.1-95	(adults) 1-3%	1-3%	3-12%	1-10%	(adults) 5-24%	58-84%	25-56%	17-44%	0.6-2.9			
					(7yr) 660-1540	51-279	73-310	(10-12yr) 380-1420	73-455	16-194	1.4-153												
					(8yr) 690-1570	56-298	74-313																
					(9yr) 700-1600	60-313	74-312																
					(10yr) 720-1020	66-332	74-311																
					(11yr) 740-1640	69-343	73-310																

VPA: Valproate, CBZ: Carbamazepine, ZNS: Zonisamide, SKCT: Shoukenchuto.

a significantly decreased IgA level and slightly decreased IgG level (Table **1**). Further immunological examinations revealed that he was deficient in IgA, IgG2, and IgG4. The levels of IgG2 against both *Hemophilus influenzae* and *Streptococcus pneumoniae* were also markedly decreased. The levels of his serum IgA were within the normal range during valproate medication, but the levels decreased below the normal range after 7 months of carbamazepine medication (Fig. **1**). He was diagnosed as having carbamazepine-related immunoglobulin deficiency as we previously described in detail [1]. Carbamazepine was replaced with zonisamide, but he still experienced recurrent enterocolitis and otitis media and his immunoglobulin levels did not normalize (Fig. **1**, Table **1**).

In addition to susceptibility to infections, he always complained of general fatigue and loss of appetite, although he had sufficient rest and sleep. Physical examination revealed that his lower eyelids were dark colored and his abdominal tension was weak. He was found to have general asthenia according to the conventional Chinese medicine diagnosis as compatible with the indication of Shoukenchuto (SKCT) (delicate constitution in childhood, fatigue, nervousness, and chronic gastroenteritis). We prescribed SKCT extract granules (TJ-99, TSUMURA & Co, Japan) as 5.0 g/day (0.15g/kg/day), expecting an improvement of his general asthenia itself, not the infections. SKCT (TJ-99) contains a dried extract of the mixed crude drugs (peony root, cinnamon bark, jujube, glycyrrhiza, and ginger) and maltose.

As we expected, he no longer complained of general fatigue and loss of appetite, and the dark color of his lower eyelids almost disappeared. In addition to these improvements, surprisingly, he did not suffer from enterocolitis or otitis for 6 months after medication with SKCT, not requiring any other treatment such as antibiotics (Fig. **1**). Immunological examinations after the treatment revealed that his serum IgG2, IgG4 and IgA levels still remained very low, but the total IgG level, and the number of circulating IgA-, IgM-, and IgD-positive B cells increased. In addition, the numbers of CD3-, CD4-, and CD8-positive cells increased, while that of CD19-positive cells decreased (Table **1**). Lymphocyte proliferation assays by mitogens remarkably increased compared with the values before SKCT medication.

DISCUSSION

In vitro and *in vivo* experiments showed that Japanese herbal medicine (Kampo) has many kinds of effects on the immune system [2], but the effect of SKCT has not been elucidated well. In a child with recurrent bronchitis, pneumonia, and enterocolitis, SKCT decreased the incidence of these diseases. Immunological examinations showed a low CD8-positive cells before treatment (CD3: 60.5%, CD4: 47.9%, CD8: 10.0%, CD4/CD8: 4.8), and the percentage normalized after the treatment (CD3: 68.1%, CD4: 47.9%, CD8: 19.2%, CD4/CD8: 2.5) [3].

Miyakawa *et al*. [4] also reported the effects of Kampo medicine on a T cell subset in 11 children with general asthenia, which was represented by susceptibility to respiratory infection or enterocolitis. Shou-sai-ko-to (0.2g/kg) was administered to six children with a low percentage of CD4-positive cells, while SKCT (0.4g/kg) was given to five patients with a low percentage of CD8-positive cells. All the patients showed clinical improvement and the percentages of their T cell subsets normalized. The results suggested the usefulness of T cell subset measurement for drug selection in addition to the conventional diagnostic classification for Chinese medicine.

Our patient was treated with SKCT for his general asthenia, not for immunological abnormalities, but his susceptibility to infection markedly improved. The increase in the T cell percentage, not of the B cell percentage, in our patient suggests the importance of regulatory function of T cells for clinical improvement. The findings in our case and the previously reported cases suggest the usefulness of Japanese herbal medicine or Chinese medicine as an alternative or a supportive therapy for patients with immunological abnormalities. However, further clinical and experimental studies should be performed to clarify the mechanisms.

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