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Short communication

Efficacy of diflunisal on autonomic dysfunction of late-onset familial amyloid polyneuropathy (TTR Val30Met) in a Japanese endemic area

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ABSTRACT

Objective: To evaluate the long-term efficacy and safety of diflunisal in late-onset familial amyloid polyneuropathy (FAP) in a Japanese endemic area.
Methods: Consecutive six FAP patients (mean age: 65.8 ± 7.3 years) with a transthyretin (TTR) Val30Met mutation from an endemic area of late-onset FAP were prospectively recruited to an open label study with oral diflunisal (250 mg twice a day). We evaluated clinical symptoms, Kumamoto FAP score, modified body mass index (mBMI), Medical Research Council sum score, nerve conduction studies (NCS), electrocardiogram (ECG), ECG Holter monitor test, echocardiography, and ^{123}iodine-metaiodobenzylguanidine (^{123}I-MIBG) myocardial scintigraphy.
Results: One patient ceased to take diflunisal because of hematuria which was reversible. The other five patients were treated with diflunisal for 3–5 (4.4 ± 0.9 years) years. Autonomic symptoms (orthostatic hypotension and gastrointestinal symptoms) disappeared after treatment in two of the four patients with the symptoms. Delayed heart to mediastinum ratio on ^{123}I-MIBG imaging, a marker of cardiac postganglionic sympathetic nerve function, increased during the three-year treatment. mBMI was maintained through observation period. While, motor and sensory symptoms, Kumamoto FAP scores, and data on NCS gradually deteriorated.
Conclusion: Diflunisal might be effective especially for autonomic dysfunction in late-onset FAP with a TTR Val30Met mutation.

1. Introduction

Familial amyloid polyneuropathy (FAP) is an autosomal dominant disease associated mainly with mutations of the transthyretin (TTR) gene (*TTR*). More than 100 mutations of *TTR* have been reported [1], and the most common mutation causing FAP is substituting methionine for valine at position 30 (Val30Met). FAP is characterized by progressive sensorimotor neuropathy with autonomic dysfunction, weight loss, gastrointestinal tract disorders, and frequent cardiac and renal involvement [2–4].

Mutations in *TTR* destabilize the tetramer, facilitating dissociation, the initial rate-limiting step in amyloidgenesis [5]. Because the most of amyloidgenic TTR is secreted by the liver, liver transplantation (LT) is widely used to treat FAP patients [6]. Diflunisal and tafamidis stabilize transthyretin tetramers and prevents amyloid fibril formation *in vitro* [7]. Recently, clinical therapeutic effects of diflunisal [8] and tafamidis [9] on FAP with a Val30Met mutation have been reported. Recent studies reported the longer-term efficacy and also the efficacy on late-onset patients of tafamidis [10,11]. However, the long-term efficacy and safety of diflunisal in late-onset FAP have not been determined as yet.

There are several endemic foci of FAP with TTR Val30Met in Portugal [12], Sweden [13], and Japan [14,15]. FAP patients with a TTR Val30Met mutation in Sweden are late-onset [16], however those in Portugal are early-onset [17]. In Japan, those in Nagano and Kumamoto prefectures are mostly early-onset, and, on the other hand, those in an endemic

Abbreviations: ATTR, transthyretin-related amyloid; AV, atrioventricular; DcT, deceleration time; E/A ratio, ratio of mitral peak velocity of early filling to mitral peak velocity of late filling; E/e′ ratio, ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e′); EF, ejection fraction; FAP, familial amyloid polyneuropathy; H/M, heart to mediastinum; ^{123}I-MIBG, ^{123}iodine-metaiodobenzylguanidine; IVST, interventricular septal thickness; LAD, left atrial dimension; LT, liver transplantation; LV, left ventricular; mBMI, modified body mass index; MRC, Medical Research Council; NCS, nerve conduction studies; OH, orthostatic hypotension; PWT, posterior wall thickness; TTR, transthyretin; *TTR*, transthyretin gene.

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Table 1
The demographic and clinical data of the FAP patients with a TTR Val30Met mutation.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex	Male	Female	Male	Male	Male	Female
Age at disease onset (years)	73	64	50	66	58	45
Age at starting diflunisal (years)	77	67	56	70	63	62
Duration from onset to starting diflunisal	4	3	6	4	5	17
Age after treatment (years)	83	72	61	71	68	64
Disease duration from onset to the end of treatment (years)	10	8	11	5	10	19
Stage of FAP at starting diflunisal[a]	1	2	2	1	1	1
Stage of FAP after the treatment[a]	2	2	2	1[b]	1	1
Kumamoto score at starting diflunisal[c]	16	12	21	21	19	12
Kumamoto score after the treatment[c]	33	25	32	21	22	10
Polyneuropathy: motor (baseline)	+	+	+	+	+	+
Polyneuropathy: sensory (baseline)	+ (FA, LL)	+ (H, F)	+ (FA, LL)	+ (FA, LL)	+ (H, LL)	+ (F)
Polyneuropathy: autonomic (baseline)	+ (OH, D/C)	+ (C)	+ (OH, D/C)	+ (OH)	−	+ (OH, D/C)
Findings of electrocardiography (baseline)	AF	LAHB, AF	LAHB	ICRBBB	I° AVB	SSS
Echo: granular sparkling sign (baseline)	+	+	+	+	+	+
Echo: thickening of LV wall[d] (baseline)	−	−	−	+	+	−
TTR mutation	Val30Met	Val30Met	Val30Met	Val30Met	Val30Met	Val30Met
Biopsies demonstrating ATTR	Sural nerve	Sural nerve	Rectum	Stomach	Sural nerve	Stomach
Diflunisal treatment duration (years)	5	5	5	0.5[b]	4	3
Side effects of diflunisal	–	–	–	Hematuria	–	–

Abbreviations: AF = atrial fibrillation; ATTR = transthyretin-related hereditary amyloidosis; C = constipation; D/C = alternate of diarrhea and constipation; Echo = echocardiogram; F = foot; FA = forearm; FAP = familial amyloid polyneuropathy; H = hand; ICRBBB = incomplete right bundle branch block; LAHB = left anterior hemiblock; LL = lower leg; LV = left ventricular; OH = orthostatic hypotension; SSS = sick sinus syndrome; TTR = transthyretin; I° AVB = first degree atrioventricular block.

[a] The stage of FAP: reference [4].

[b] Patient 4 ceased diflunisal treatment, and was discontinued from follow-up, because of side effect, hematuria.

[c] Kumamoto score: reference [20].

[d] Thickening of LV wall was defined as the mean of the septal and posterior wall thickness which increased by more than 12 mm.

focus of our Ishikawa prefecture [18] and in non-endemic areas [19] are late-onset. In older patients with late-onset FAP, LT is seldom indicated. Thus, we conducted this study to examine the long-term efficacy and safety of diflunisal for late-onset FAP in our endemic area.

2. Methods

This was the open-labeled intervention study without a control group carried out in an endemic district in Japan where most of FAP patients were late-onset [18]. We prospectively investigated the safety and effects of diflunisal in FAP patients with a TTR Val30Met mutation who were admitted to our university hospital during 2004 and 2013. This study was approved by the medical ethical committee of our university.

We recruited consecutive six FAP patients with a TTR Val30Met mutation from separate kinships. The diagnosis was confirmed by positive family history, clinical and neurophysiological examinations, tissue biopsies demonstrating TTR-immunoreactive amyloid deposits, and *TTR* analysis.

After obtaining written informed consent, we started treatment with oral diflunisal (250 mg twice a day) (TEVA Pharmaceutical Industries, Ltd.). At baseline and after the treatment, we evaluated clinical symptoms, the stage of FAP [4], Kumamoto FAP score [20], modified body mass index (mBMI), grip power, Medical Research Council (MRC) sum score, nerve conduction studies (NCS), electrocardiogram (ECG), ECG Holter monitor test, echocardiography, and ^{123}iodine-metaiodobenzylguanidine (^{123}I-MIBG) imaging. To evaluate safety and adverse effects of diflunisal, we regularly monitored complete blood count, serum chemistries, and urinalysis after starting diflunisal treatment.

The stage of FAP is to evaluate activities of daily life, ranging from stages 1 (walking without help) to 3 (bedridden) [4]. Kumamoto score is the clinical scale for FAP to assess motor, sensory, and autonomic dysfunction, and organ damage, and higher scores reflect increasing disease severity [20]. MRC sum score evaluates 12 muscle strength by manual testing [21]. mBMI is the product of serum albumin concentration (g/L) and body mass index that correlates with survival in FAP [22].

NCS was performed with Neuropack MEB2200 (Nihon Kohden, Tokyo, Japan). We assessed bilateral median, ulnar, tibial, peroneal, and sural nerves with following parameters in NCS: compound muscle action potentials (CMAPs), sensory nerve action potentials (SNAPs), distal latencies, and motor and sensory conduction velocities. As previously described [10], the motor and the sensory sum score were calculated.

Echocardiography was acquired with iE33 Ultrasound (Philips Electronics, Tokyo, Japan) or Aplio XV (Toshiba, Tokyo, Japan), and markers as shown in Table 2 were measured. ^{123}I-MIBG myocardial scintigraphy is non-invasive assessment of the postganglionic sympathetic nerve endings [23]. This imaging was acquired with a dual-head gamma camera (Symbia T6, Siemens, Erlangen, Germany) equipped with low–medium-energy general-purpose collimators. The early and delayed heart to mediastinum (H/M) ratios and washout rate were measured using the semiautomatic algorithm for determining mediastinal region of interest to obtain reproducible data, as previously described [24].

Statistical analyses were performed with paired *t* test using software package StatView version 5.0. p values <0.05 were considered significant.

3. Results

3.1. Patient characteristics at baseline

Demographic and clinical data are summarized in Table 1. Mean age at onset was 59.3 years, and mean age at starting diflunisal treatment was 65.8 years. Disease duration from onset to starting diflunisal ranged from 3 to 17 years (average ± SD: 6.5 ± 5.2 years).

All the patients showed polyneuropathies with motor, sensory, and autonomic dysfunction, cardiac arrhythmia or conduction block on

Fig. 1. Changes of Kumamoto score (A), Medical Research Council (MRC) sum score (B), grip power sum of both hands (kg) (C), modified body mass index (mBMI) (D), and early (E) and delayed H/M ratios (F), and washout rate (G) in ^{123}I-MIBG myocardial scintigraphy during diflunisal treatment for up to five years.