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H. 知的財産権の出願・登録状況（予定含む）

（特許取得・実用新案登録・その他）

なし

厚生労働科学研究費補助金（難治性疾患克服研究事業）
研究報告書

Torsin A の細胞内動態

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研究要旨

TorsinA の変異が DYT1 ジストニアをもたらす。これまでは変異ジストニアは細胞内分布異常をきたすとされた。今回は TorsinA を蛍光タンパク質でラベルし細胞内分布を検討した。TorsinA は明瞭な核膜・小胞体分布を示したが変異体との差は見られずこれまでの報告を確認できなかった。

A. 研究目的

TorsinA の 302/303 のグルタミン酸が失われることが DYT1 ジストニアの本態であることが Ozelius らにより 1997 年に明らかになった。以来、TorsinA については AAA+タンパク質であり核膜と小胞体に分布し、これに由来するシナプス小胞が変異により少なくなるため、DYT1 ジストニアが発症すると考えられるようになった。今回はその仮説の検証のはじめとして、TorsinA を 2 種の蛍光タンパク質でラベルし細胞内動態追跡を試みた。

B. 研究方法

Tor1A を新たにクローニングし、302/303 のグルタミン酸の欠失する変異を作成した。TorsinA と AcGFP 、DsRed-monomer (Clontech) の 2 種の蛍光タンパク質との融合タンパク質をそれぞれ作成し Cos7 細胞と SHSY5Y 細胞で発現させた。小胞体を 2 種の ER マーカータンパク質で同時に発現させ蛍光顕微鏡で観察した。

C. 研究結果および考察

AcGFP で作成した融合タンパク質は核周囲に集積し、小胞体には微量に分布するだけであった。DsRed-monomer との融合タンパク質は核膜と小胞体に分布した。この分布パターンは変異のあるなしで有意な差は得られなかった。

E. 結論

TorsinA の蛍光タンパク質ラベルは明瞭な核膜・小胞体分布を示したが変異体との差は見られずこれまでの報告を確認できなかった。

G. 研究発表

1. 論文発表
   なし
2. 学会発表
   なし

H. 知的財産権の出願・登録状況

なし

厚生労働科研費補助金（ジストニアの診断及び治療法の更なる推進に関する研究事業）
総合研究報告書

ジストニア患者の満足度に関するアンケート調査および ジストニア診療とケアマニュアルの作成

（分担） 研究者　堀内正浩　川崎市立多摩病院神経内科部長
聖マリアンナ医科大学神経内科准教授

要旨：ジストニア患者の満足度を知るためにアンケート調査を行った。診断、治療とも十分ではなく、医師および社会の認知度も低かった。また、ジストニア患者を啓蒙する目的で、「ジストニア診療とケアマニュアル」を作成した。

A．研究目的

ジストニア患者の満足度を知るために、①病名病歴等、②治療、③日常生活につきアンケート調査を行った。また、啓蒙する目的で「ジストニア診療とケアマニュアル」を作成した。

B．研究方法

NPO法人ジストニア友の会(DFA)会員および聖マリアンナ医科大学神経内科ジストニア外来受診中の患者計300名に対してアンケート調査を行った。アンケートは①病名・病歴等、②治療、③日常生活につき計64問ある。DFA会員にはアンケートと同意書を郵送し、アンケートと同意書を手渡し、同封した返信用封筒で返送してもらった。ジストニア診療とケアマニュアルの目次は、①ジストニアとは、どんな病気ですか？、②どのようにして診断されますか？、③どうして起こるのでしょう？、④どんな人がなるのですか？、⑤ジストニアは命にかかわる病気ですか？、⑥どんな治療がありますか？、⑦ジストニア症状別Q&A (a)眼瞼痙攣、(b)痙攣性発声障害、(c)痙性斜頸、(d)書痙、(e)音楽家のジストニア、(f)下肢ジストニア、(g)スポーツにかかわるジストニア、(h)遅発性ジストニア、(i)ジストニアを起こす疾患、⑧ジストニア患者へのアドバイス、コラム、⑨関連サイト、である。

C．研究結果

①一次性(原因不明)が二次性(薬剤性、外傷性等)に比べ多かったが、診断がついていない例も多く含まれていた。

②治療を中断している例も多く、ボツリヌス毒素療法をしている患者でも症状の改善度は低く、満足度も低かった。脳深部刺激(DBS)等の外科手術を行った患者はごく一部だった。

③ジストニアに対する職場の理解度は低く、社会保障制度も十分に受けられていない例が多かった。

④「ジストニア診療とケアマニュアル」が診断と治療社から出版された。

E．結論

ジストニア患者は日常生活に不便を感じていることが殆どで、社会保障に対する要求は高かった。また、平易な文書で書かれた患者向けのマニュアルも必要だと考えた。

II. 研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
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堀内正浩		梶　龍兒	ジストニア診療とケアマニュアル	診断と治療社	東京	2011	
坂本　崇	A 型ボツリヌス毒素療法	山口徹 北原光夫 福井次矢	2011 今日の治療指針	医学書院	東京	2011	767
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III. 研究成果の刊行物・別刷

Parkinsonism and Related Disorders 17 (2011) 123–125

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Short communication

Bilateral pallidal deep brain stimulation in primary Meige syndrome☆

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ARTICLE INFO

Article history:
Received 16 April 2010
Received in revised form
16 November 2010
Accepted 18 November 2010

Keywords:
Meige syndrome
Deep brain stimulation
Globus pallidus internus
Dystonia

ABSTRACT

Primary Meige syndrome is an idiopathic movement disorder that manifests as craniofacial and often cervical dystonias. Deep brain stimulation (DBS) of the globus pallidus internus (GPi) has emerged as a powerful surgical option in the treatment of primary generalized or segmental dystonia. However, the experience with GPi-DBS in Meige syndrome is limited. We followed 5 patients with disabling Meige syndrome treated by bilateral GPi-DBS for 49 ± 43.7 (mean ± SD) months. All patients were assessed before surgery and at the last follow-up after surgery using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) which includes both the movement and disability scales. Bilateral GPi-DBS produced a sustained and long-lasting improvement in dystonia symptoms associated with Meige syndrome. At the last follow-up, the mean scores of BFMDRS movement and disability scales improved significantly by 84 ± 6.8% (range, 75–94%) and 89 ± 8.1% (range, 80–100%), respectively. Bilateral pallidal stimulation is a beneficial therapeutic option for long-term relief of the disabling dystonia symptoms in Meige syndrome.

1. Introduction

Primary Meige syndrome is an idiopathic dystonia that involves craniofacial and often cervical muscles. This adult-onset movement disorder manifests as blepharospasm and oromandibular dystonia, but dystonia may also occur in the upper extremities, trunk, and neck [1,2]. Meige syndrome can be disabling despite the best medical therapy. Botulinum toxin injections constitute the standard treatment for Meige syndrome, but its effectiveness often diminishes over time. Deep brain stimulation (DBS) of the globus pallidus internus (GPi) has emerged as a powerful surgical option in the treatment of primary generalized and segmental dystonias [3], and interest in the use of GPi-DBS for refractory dystonia symptoms in Meige syndrome is increasing [4–7]. However, the beneficial effects of GPi-DBS in patients with Meige syndrome remain to be established, because the data currently available is based on a small series of patients with short-term follow-up. To further elucidate the therapeutic efficacy of pallidal stimulation, we assessed surgical outcome in 5 patients suffering from disabling Meige syndrome who underwent bilateral GPi-DBS.

2. Methods

2.1. Subjects

The clinical characteristics of the patients included in this study are summarized in Table 1. None of the patients had a family history of dystonia or prior exposure to neuroleptics, and their preoperative brain magnetic resonance images appeared normal. Before surgery, written informed consents were obtained from all patients and their families. At the time of surgery, the mean age of the patients was 65 ± 7.2 (mean ± SD) years (range, 54–72 years) and the mean disease duration was 12 ± 4.2 years (range, 7–18 years).

2.2. Assessment instruments

All patients were assessed before surgery and at the latest follow-up after surgery using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), which includes both the BFMDRS-I (Movement Scale) and BFMDRS-II (Disability Scale) [8]. The mean follow-up period was 49 ± 43.7 months. Statistical analyses were performed using the Mann–Whitney *U* test. A p value < 0.05 was considered statistically significant.

☆ The review of this paper was entirely handled by an Associate Editor, Eng-King Tan.

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doi:10.1016/j.parkreldis.2010.11.013

Table 1
Characteristics of patients with Meige syndrome who underwent bilateral pallidal stimulation.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Mean ± S.D.
Age (yr)/Sex	54/M	67/F	61/F	72/M	69/M	65 ± 7.2
Age at onset (yr)	44	53	43	65	53	52 ± 8.9
Duration of disease (yr)	10	14	18	7	13	12 ± 4.2
Follow-up after surgery (months)	30	40	124	43	10	49 ± 43.7
Total number of hospital visits	17	25	122	21	6	38 ± 47.4
Electrode						
Right	2(−)C(+)	0(−)1(−)C(+)	1(−)3(+)	0(−)1(−)C(+)	0(−)C(+)	
Left	1(−)C(+)	0(−)1(−)C(+)	1(−)3(+)	0(−)1(−)C(+)	0(−)C(+)	
Amplitude (V)						
Right/Left	1.7/1.7	1.0/1.0	3.9/3.6	2.9/2.8	3.5/3.5	2.6 ± 1.1
Pulse width (μS)	450	450	450	210	400	392 ± 98.1
Frequency (Hz)	90	130	60	80	60	84 ± 27.2
BFMDRS-I (Movement Scale) (max = 120)						
Preoperatively	8	10	35	27	31	22 ± 12.4
Postoperatively	2	1.5	5	5	2	3 ± 1.7
Percent improvement (%)	75	85	86	81	94	84 ± 6.8
BFMDRS-II (Disability Scale) (max = 30)						
Preoperatively	3	5	23	13	12	11 ± 7.9
Postoperatively	0	1	4	1	1	1 ± 1.5
Percent improvement (%)	100	80	83	92	92	89 ± 8.1

BFMDRS, Burk-Fahn-Marsden dystonia rating scale; PW, pulse width (μS); freq, frequency (Hz); M, male: F, female; yr, years.

2.3. Surgical procedure

Bilateral GPi-DBS surgery was carried out as we previously reported [9]. Under general anesthesia with propofol, quadripolar DBS electrodes (Model 3387; Medtronic Inc., Minneapolis, MN) were implanted into the bilateral GPi. Using intraoperative microelectrode recordings, the ventral edges of the most ventral contacts (contact 0) were located at the ventral margin of the GPi. As stimulation tests over the course of 3 or 4 days confirmed the beneficial effects of pallidal stimulation, the DBS electrodes were connected to programmable pulse generators (Soletra, Medtronic) implanted subcutaneously in the subclavicular region. Outcomes were assessed at follow-up visits every 1 or 2 months after discharge.

3. Results

3.1. Stimulation settings

For all patients, optimal results were obtained at the final stimulator settings with the mean amplitude of 2.6 ± 1.1 V (range, 1.0–3.9 V), mean frequency of 84 ± 27.2 Hz (range, 60–130 Hz), and pulse width of 392 ± 98.1 μs (range, 210–450 μs) (see Table 1). We applied a continuous monopolar mode using 1 or 2 active contacts in all patients except patient 3, for whom a bipolar mode with contacts 1 (cathode) and 3 (anode) was used.

3.2. Assessment with BFMDRS

As shown in Table 1, the mean follow-up period was 49 ± 43.7 months (range, 10–124 months); 4 of the 5 patients were followed for more than 30 months. At the latest follow-up, dystonia symptoms had improved markedly in all patients. The mean scores for BFMDRS movement and disability scales improved significantly by 84 ± 6.8% (range, 75–94%) ($p = 0.009$) and 89 ± 8.1% (range, 80–100%) ($p = 0.015$), respectively (Table 1). All BFMDRS movement (Table 2) and disability (Table 3) subscales significantly improved after pallidal stimulation except for subscales of "upper limbs" and "feeding". As in primary generalized and segmental dystonias [3], phasic (mobile) orofacial dystonia and blepharospasm improved earlier and to a greater degree than fixed cervical dystonia. The time required for response of blepharospasm to GPi-DBS varied from a few seconds to days. Speech disturbance caused by spasmodic dysphonia and/or oromandibular dystonia also responded well to pallidal stimulation in all the patients (Table 3). Postoperative adverse effects of chronic stimulation could be reversed by adjusting the stimulus parameters. No permanent morbidity occurred because of the operation or stimulation.

Table 2
BFMDRS movement subscales in patients with Meige syndrome who underwent bilateral pallidal stimulation.

Movement scale								
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Mean	Range	
Before surgery (range)								
Eyes (0–8)	2	6	8	6	8	6	2–8	
Mouth (0–8)	3	2	8	6	6	5	2–8	
Speech and swallowing (0–16)	3	2	12	9	9	7	2–12	
Neck and trunk (0–24)	0	0	6	6	8	6.7	6–8	
Upper limbs (0–32)	0	0	1	0	0	1	1	
Total	8	10	35	27	31	22.2	8–35	
After surgery								*p* value
Eyes (0–8)	1	1	1	0.5	0	0.7	0–1	0.008
Mouth (0–8)	1	0.5	1	0.5	0	0.6	0–1	0.008
Speech and swallowing (0–16)	0	0	2	2	0	0.8	0–2	0.013
Neck and trunk (0–24)	0	0	1	2	2	1.7	1–2	0.043
Upper limbs (0–32)	0	0	0	0	0	0	0	
Total	2	1.5	5	5	2	3.1	1.5–5	0.009

Statistical analyses were performed using the Mann–Whitney *U* test.

Table 3
BFMDRS disability subscales in patients with Meige syndrome who underwent bilateral pallidal stimulation.

Disability scale								
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Mean	Range	
Before surgery (range)								
Speech (0–4)	3	2	4	1	1	2.2	1–4	
Writing (0–4)	0	1	3	1	1	1.5	1–3	
Feeding (0–4)	0	0	3	2	1	2	1–3	
Eating and swallowing (0–4)	0	0	3	2	3	2.7	2–3	
Hygiene (0–4)	0	1	3	2	2	2	1–3	
Dressing (0–4)	0	1	3	2	2	2	2–3	
Walking (0–6)	0	0	4	3	2	3	2–4	
Total	3	5	23	13	12	11.2	3–23	
After surgery (range)								*p* value
Speech (0–4)	0	1	1	0	0	0.4	0–1	0.022
Writing (0–4)	0	0	1	0	0	0.3	0–1	0.04
Feeding (0–4)	0	0	0	1	0	0.3	0–1	0.072
Eating and swallowing (0–4)	0	0	0	0	0	0	0	0.034
Hygiene (0–4)	0	0	0	0	0	0	0	0.013
Dressing (0–4)	0	0	1	0	0	0.3	0–1	0.025
Walking (0–6)	0	0	1	0	1	0.7	0–1	0.046
Total	0	1	4	1	1	1.4	0–4	0.015

Statistical analyses were performed using the Mann–Whitney *U* test.

4. Discussion

Clinical studies in patients with primary generalized or segmental dystonia have shown the beneficial effects of bilateral GPi-DBS for both motor symptoms and disability caused by dystonia [3]. However, experience with GPi-DBS in other forms of dystonia such as Meige syndrome is limited. Moreover, long-term outcome of patients with Meige syndrome treated with GPi-DBS remain to be elucidated. In this study, we showed that bilateral pallidal stimulation produced a long-lasting suppression of dystonia in 5 patients with primary Meige syndrome. The mean improvement (over 80%) in motor symptoms was comparable, with respect to scores of both BFMDRS motor and disability scales (Table 2), to the results obtained in patients with primary generalized or segmental dystonia [10], and in patients with tardive dystonia [11]. Our results also showed that speech difficulties caused by spasmodic dysphonia and/or oromandibular dystonia in Meige syndrome responded well to pallidal stimulation.

Dystonia is a complex clinical syndrome due to a wide range of etiologies. The pathogenesis of primary Meige syndrome remains unknown. However, it has been suggested that the basal ganglia interconnecting the cortico-striato-pallido-thalamic circuits are involved in models of the pathophysiology of Meige syndrome [5]. The present study provides clinical evidence that dystonia symptoms in primary Meige syndrome could be markedly alleviated by electrostimulation of the GPi, one of the output nuclei of the basal ganglia, and suggests that this movement disorder may result from the basal ganglia dysfunction. Multimodal medical treatments that include botulinum toxin injections are used to treat Meige syndrome, but their therapeutic efficacy has been found to vary across patients and often decreases over time. As reported here, we observed continuous bilateral GPi-DBS to be a safe surgical therapy for producing a sustained and long-term improvement in the dystonia symptoms and functional disabilities of patients with primary Meige syndrome. Recently, an important observation was made that while disease duration can be a good predictor of the outcome of pallidal stimulation in patients with primary dystonias, no particular predictive value should be assigned to age at onset, age at surgery, severity of disease, DYT1 status or the presence of phasic or tonic involuntary movements [12]. The mean duration of disease in our patients with Meige syndrome was greater than 10 years, and a better general outcome of pallidal stimulation might be expected in patients with a shorter duration of this disease. In conclusion, we suggest that patients with disabling dystonia symptoms associated with primary Meige syndrome can be good candidates for treatment with bilateral pallidal stimulation.

Acknowledgements

This work was supported by grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan (grant-in-aid for Scientific Research, 20591025).

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Parkinsonism and Related Disorders 17 (2011) S25–S27

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/parkreldis

New and emerging indications of botulinum toxin therapy

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Keywords:
Botulinum toxin
Therapy
A1
A2
Pain
Epilepsy
Spasticity

A B S T R A C T

Botulinum neurotoxin (BoNT) is composed of the heavy chain with the receptor-binding site and the translocation domain and the light chain with endopeptidase activity that cleaves the SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor) complex, an essential molecule for membrane fusion. Its extraordinarily high toxicity depends on the affinity of the receptor-binding site to the receptor located inside the synaptosome. The membrane fusion mechanism is important not only in neurotransmitter release at the nerve terminals but also in the expression of pain receptors on the cell surface. Based on these mechanisms, BoNT is increasingly used for varieties of conditions including cosmetic uses, muscle hyperactivity, hyperhydrosis, pain, overactive bladder and epilepsy. It will become a major arm of neuromodulating treatments for neurological diseases. A part of this toxin, such as the heavy chain, may become a novel drug-delivery system for neurodegenerative diseases.

1. Advances in botulinum toxin research

Botulinum neurotoxins (BoNTs) are produced by anaerobic bacteria of the *Clostridium* group and are the most potent toxins known to date [1]. There are seven serotypes of BoNTs, indicated by letters from A to G. Each toxin is composed of a heavy (H, 100 kDa) and a light chain (L, 50 kDa) linked by a disulphide bond and non-covalent interactions. The carboxy terminus of the heavy chain (HC) binds with extraordinary specificity to nerve terminals. Following receptor-mediated endocytosis and acidification of the endosome, the amino-terminal portion of the heavy chain (HN) translocates the L chain across the vesicular membrane into the cytosol. The L chain acts as a Zn^{2+}-dependent endopeptidase to cleave essential protein components of the neurotransmitter release machinery, the SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor) proteins. This disrupts Ca^{2+}-triggered fusion of synaptic vesicles (SVs) with the plasma membrane [2].

The receptors of BoNTs have been clarified recently: serotype B BoNT binds to synaptotagmin II^3 and serotype A to SV2 [4], both of which are located on the inner surface of the synaptosome. BoNT also recognises the ganglioside moiety (trisialoganglioside, GT1b) on the surface of the cell membrane, which determines the target selectivity [3]. These findings explain the activity-dependent action of the toxin: BoNTs affect the synapses most active in releasing the neurotransmitters because they can access the synapses or neuromuscular junctions with the receptors inside the vesicle. It has been known that the action of BoNTs is optimised when the muscles are activated immediately following the injection [5]. This action is in contrast with the neurolytic therapies, such as phenol injections, which affect all the nerve endings irrespective of the activities, resulting in unwanted weakness of the injected muscles. By contrast, BoNTs abolish only twitching muscles in case of hemifacial spasms. This is relevant with other involuntary movements or spasticity, where active engagement in the affected movement or posture is encouraged after injections, to attain the maximum benefit of BoNTs.

The potency of the toxin is mostly due to its very high affinity to the receptors. The receptor-binding capability of the heavy chain is now being explored for development of the drug-delivery system to neurons after replacing the L chain with other moieties [6]. Such an attempt may be fruitful for the development of drugs for amyotrophic lateral sclerosis, if the L chain is substituted by neurotrophic factors.

Types A, B and F toxins have been used for clinical settings in the past [7]. Currently, types A and B are marketed. Among type A toxins, four subtypes (A1–A4) exist, and all the marketed toxins are from subtype A1. Recently, type A2 toxin has been used in animals [8] and showed greater potency in producing weakness and less spreading into uninjected muscles than conventional A1 toxin. It was also shown that type A toxins affects central synapses, and subtype A2 has less central actions than A1 because of the less retrograde transport of the toxin to the spinal cord [9].These findings may lead to a BoNT preparation used for larger muscles, such as those in the lower extremities in patients with spasticity.

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1353-8020/$ – see front matter © 2011 Published by Elsevier Ltd.
doi:10.1016/j.parkreldis.2011.06.017

2. Clinical indications

Indications of BoNTs have been constantly expanded in the past decade.

BoNTs' most popular use is for cosmetic purposes. It is widely accepted that wrinkles on the face go away almost indefinitely after the injection, but the exact mechanism is still elusive.

2.1. Muscle hyperactivity

By far the most important use in neurological diseases is for muscle hyperactivity, including dystonia and spasticity. Focal dystonias, such as blepharospasm and cervical dystonia, are the best indications among dystonias. Task-specific dystonias including writer's or musician's cramp are less optimal [10] because of the unwanted weakness for the tasks. Larger doses are required for treating truncal or lower-extremity dystonias, and new preparations, such as the A2 subtype, might be relevant. Generalised or segmental dystonias are treated more efficaciously by surgical manoeuvres, such as deep-brain stimulation of bilateral GPi.

Hemifacial spasms are also good indication of BoNTs, and decompression surgeries are becoming obsolete as the first-line treatment. The dose required is usually less than that in blepharospasm, and the injection interval is longer.

Spasmodic dysphonia, a dystonia involving vocal-cord muscles, is also a superb indication of BoNT. A special injection technique for this is needed.

Spasticity is probably one of the most prevalent and important health problems in developed nations. Up to 65% of the patients who survived stroke suffer from it. Cost of care for those patients far exceeds 2,000,000,000,000 yen or 20 billion US dollars per year in Japan. Until 2004, a few randomised controlled trials have reported some promising results in support of reduced muscle tone following BoNT injections [11]. Further research incorporating larger sample sizes, rigorous methodology, measurement of upper-limb function and functional outcomes was essential. Since then, there have been several large-scale clinical trials for upper-limb spasticity showing functional improvements [12]. A recent study in the post-stroke lower-limb spasticity also reported markedly significant improvements in the modified Ashworth scale [13]. Functional improvements were only attained by repeated injections. By now, uses in spasticity in upper and lower-limbs have been approved in UK, France, Germany and Japan, and use for upper-limb was approved by the Food and Drug Administration (FDA) in USA.

Interestingly, patients with upper-limb spasticity often improve their motor disturbance after BoNT injection and rehabilitation almost permanently, without the need for further injections. This is unlike those with hand dystonia, who need repeated injections to maintain the benefit. It is argued that BoNT may enhance spinal synaptic reorganisation directly by its central action or indirectly through alteration of muscle afferents [14]. Another possibility is that release of the affected hand into active movements may reverse anomalous interhemispheric inhibition from the unaffected cortex to the affected.

Because the sudomotor sympathetic fibres are also cholinergic, BoNTs have been used for controlling hyperhydrosis, which can occur either after skin incisures or without any known causes.

2.2. Pain

A breakthrough in the clinical application of BoNT is its use for controlling pain and migraine. BoNT was shown to decrease the expression of pain-sensitive vanilloid receptors (e.g., transient receptor potential cation channel subfamily V member 1, TRPV1), which are up-regulated in sensitised sensory neurons [15]. This is because those receptors are expressed to the cell membrane through the fusion mechanism mediated by the SNARE complex, the substrate of BoNTs.

It was accidentally found that BoNT injection into corrugator muscle for removing skin furrows brought about a decrease in the number of migraine attacks. Since then, a number of clinical trials with a small number of cases and modest doses have resulted in equivocal results for migraine. Recently, clinical trials with larger number of cases and doses of BoNT have successfully reduced the number of attacks [16–18], followed by its approval in UK and USA.

Intractable pain or complex regional pain syndrome is another important indication recently added. Patients with these conditions present with oedematous, painful and immobile limb with skin areas with allodynia, or abnormally induced pain after light touch. Repeated injections into these areas subcutaneously result in gradual improvement of allodynia and pain, followed by decreased oedema and increased mobility. It was also found that post-stroke pain including thalamic pain also responds to subcutaneous BoNT injections made into areas with allodynia [19].

2.3. Overactive bladder (OAB)

Urinary problems are very common in the elderly. Many people are affected by urinary urgency, which can be highly bothersome. Urgency is the cornerstone symptom of overactive bladder (OAB), commonly occurring in conjunction with urinary frequency and nocturia. Once other medical causes of similar symptoms have been excluded, first-line OAB management comprises fluid-intake advice and bladder training, supplemented by antimuscarinic drugs, if necessary. BoNTs are currently explored as an alternative therapy [20,21]. The injection into the inner surface of the bladder was shown to down-regulate the expression of TRPV1 and muscarinic Ach receptors, which trigger destrusors. Despite the technical difficulties, this technique will be widely used for these patients in the near future.

2.4. Epilepsy

Experimental pieces of evidence suggest that BoNT suppresses glutamate release in the central nervous system (CNS). Because of its activity-dependent action, BoNT may be used for managing intractable epilepsies [22,23]. Abnormal excitation at the epileptic foci is associated with large glutamate-induced excitatory post-synaptic potentials (EPSPs) that drive cortical neurons for lateral spread. BoNT would selectively suppress these active neurons, leaving the rest of the neurons unaffected. It would therefore be expected that BoNT suppresses neurons at the foci, while the rest of the neurons function normally. This method may become a substitute for surgical resections of the affected brain tissue. The largest problem would be the drug-delivery, and stereotactic device and cerebrospinal fluid (CSF) injections are now being contemplated.

In conclusion, BoNT is increasingly used for varieties of conditions including cosmetic uses, muscle hyperactivity, hyperhydrosis, pain, OAB and epilepsy. It will become a major arm of neuromodulating treatment for neurological diseases.

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