



Comparative Study of Multimodal Therapy in Facial Palsy Patients

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Abstract

Introduction In chronic facial palsy, synkinetic muscle overactivity and shortening causes muscle stiffness resulting in reduced movement and functional activity. This article studies the role of multimodal therapy in improving outcomes.

Methods Seventy-five facial palsy patients completed facial rehabilitation before being successfully discharged by the facial therapy team. The cohort was divided into four subgroups depending on the time of initial attendance post-onset. The requirement for facial therapy, chemodenerivation, or surgery was assessed with East Grinstead Grade of Stiffness (EGGS). Outcomes were measured using the Facial Grading Scale (FGS), Facial Disability Index, House-Brackmann scores, and the Facial Clinimetric Evaluation scale.

Results FGS composite scores significantly improved posttherapy (mean-standard deviation, 60.13 ± 23.24 vs. 79.9 ± 13.01 ; confidence interval, -24.51 to -14.66 , $p < 0.0001$). Analysis of FGS subsets showed that synkinesis also reduced significantly ($p < 0.0001$). Increasingly, late clinical presentations were associated with patients requiring longer durations of chemodenerivation treatment ($p < 0.01$), more chemodenerivation episodes ($p < 0.01$), increased doses of botulinum toxin ($p < 0.001$), and having higher EGGS score ($p < 0.001$).

Conclusions This study shows that multimodal facial rehabilitation in the management of facial palsy is effective, even in patients with chronically neglected synkinesis. In terms of the latency periods between facial palsy onset and treatment initiation, patients presenting later than 2 years were still responsive to multimodal treatment albeit to a lesser extent, which we postulate is due to increasing muscle contracture within their facial muscles.

Keywords

- ▶ facial paralysis
- ▶ synkinesis
- ▶ botulinum toxins-type A
- ▶ physical therapy modalities
- ▶ surgery
- ▶ plastic

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Introduction

The constant agonistic-contraction and antagonistic-relaxation within groups of skeletal muscles, prevents the stiffening of actin-myosin cross-bridges that could result in reduced movement. However, in facial palsy when there is a prolonged period of inactivity followed by chronic overactivity within the facial muscles, thixotropy, the formation of tight cross-bridges between the actin and myosin filaments of the muscle fibers causing stiffness of the muscle, is thought to occur.¹ This phenomenon was first described in the levator palpebrae superioris muscles by Aramideh et al as a contributory factor in the development of lagophthalmos in peripheral facial palsy.² Regular passive stretching has been shown to reduce thixotropy and reoptimize the agonist-antagonistic balance and muscle function.³ This forms the initial basis of specialist facial rehabilitation following chronic lower motor neuron facial paralysis, for example, Bell's palsy.

Multimodal facial rehabilitation in the management of facial palsy includes a combination of treatment modalities. Patients are psychologically screened given the known impact of facial palsy on psychological health⁴ and offered care as appropriate.⁵ Patients with acute paralysis are given flaccid management advice including education on facial

nerve recovery, cheek taping, facial massage,⁶ eye lid stretching, and eye protection strategies. They are also taught to minimize contralateral hyperkinesis with education, stretching, and relaxation techniques. If paralysis fails to resolve patients are offered static or dynamic surgical reanimation as appropriate. Patients with urgent eye issues are referred to the oculoplastics team for consideration of platinum eyelid weight surgery and other corrective procedures as required.⁷

As recovering patients move into paresis, they commence movement reeducation work in therapy. This incorporates muscle release work due to stiffness following prolonged inactivity, education on normal facial anatomy, physiology, and function and coordinated movement practice retraining.⁸ Many patients with prolonged recovery go on to develop synkinesis.⁹ This is managed primarily in facial therapy with muscle release techniques, relaxation work, and neuromuscular retraining.¹⁰ Some patients are also offered chemodeneration⁴ to reduce synkinetic muscle activity. Those recalcitrant to both facial therapy and chemodeneration, may be offered synkinesis surgery in the form of selective neurolysis and myectomy.¹¹ See ►Fig. 1 for an overview of interventions offered in facial palsy management.

In this article, we set out to determine whether (1) a multimodal treatment approach had a significant benefit on

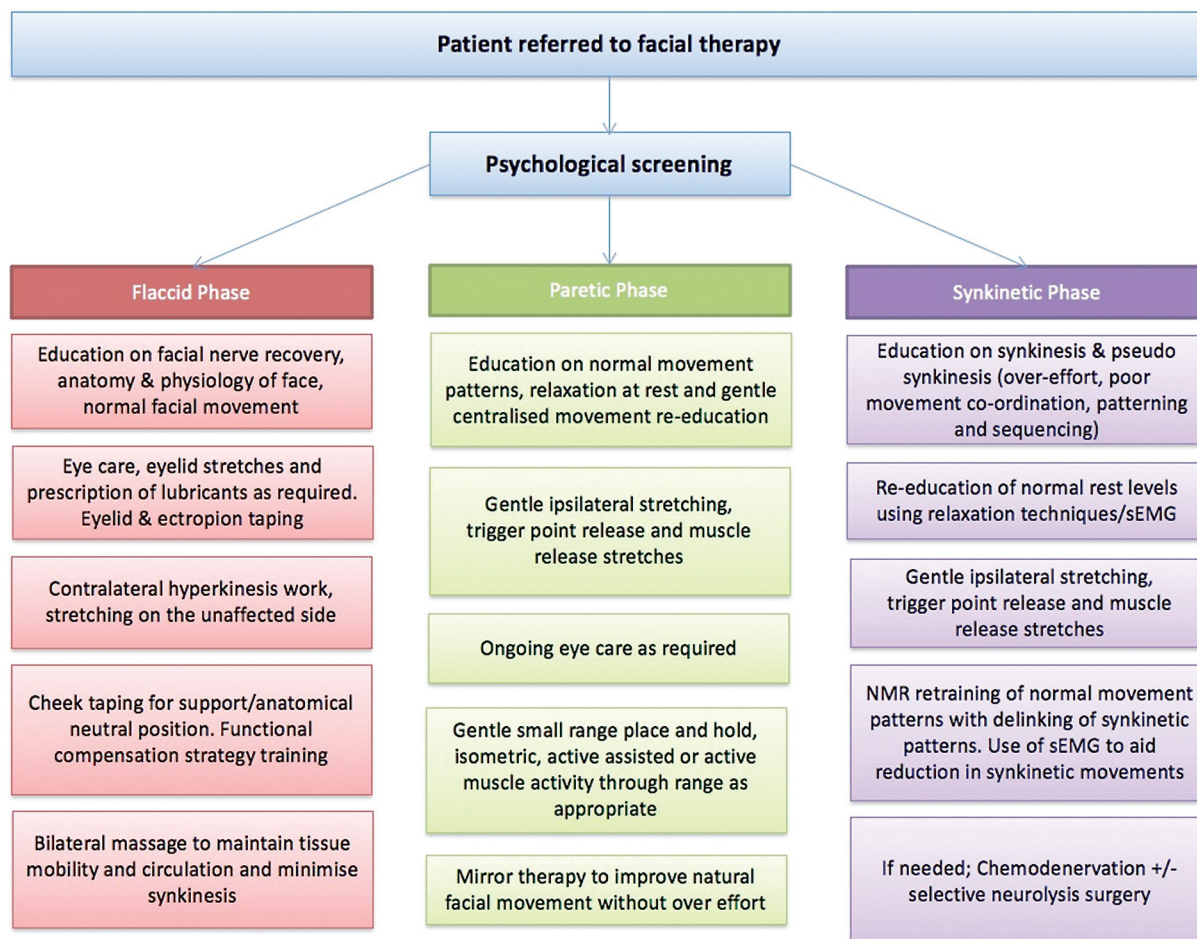


Fig. 1 A schematic illustration of the facial therapy pathway which patients in our cohort followed.

recovery in facial palsy and (2) whether earlier presentation to therapy has greater benefit in terms of rehabilitation.

Methods

A retrospective case review of 75 patients ($n=75$) was conducted at our facial palsy center over a 7-year period of follow-up (2013–2020). Patients were included if they had completed a course of specialist facial therapy rehabilitation, been discharged from this treatment arm, and had complete documentation. This study adheres to the STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) guidelines, conforms to the Helsinki guidelines on ethics, and was registered with and approved by the institutional review team from the Research and Development Department at The Queen Victoria Hospital NHS Foundation Trust prior to being conducted (IRB No.1286).

Our standardized multidisciplinary clinic management process was followed for all patients attending our facial palsy service. Patients were initially screened by the psychological therapy team to determine their mental status, given the known impact of facial palsy on psychological health.⁴ Patients were then assessed by the multidisciplinary team. The facial muscles must have a neural supply if neuromuscular retraining is to be successful.¹² Those with chronic flaccid paralysis lasting beyond 18 months who have no therapy management potential¹² were given flaccid management advice, psychological therapy as required, and surgical reanimation as appropriate. Patients with urgent eye issues were referred for ophthalmology assessment and management as required. Patients who had potential for recovery (e.g., paretic and synkinetic patients) were referred on for rehabilitation with the specialist facial therapy team.

Seventy-five patients ($n=75$) fulfilled the inclusion criteria for specialist facial therapy. To elicit the effect timing of facial therapy has on outcomes, the cohort was divided into four subsets. Group I (who presented within 6 months post-palsy), group II (between 6 and 12 months post-palsy), group III (between 1 and 2 years post-palsy), and group IV (late presentations beyond 2 years post-palsy). Seventy percent of patients recover spontaneously within 3 months whereas deficits of varying magnitude persist in the remaining 30%.¹³ Due to the potential for acute facial palsy to recover spontaneously within the first 12 weeks following neuropraxia, group I patients' results were omitted from final analysis; however, their results

and management strategies have been included for reference. Patients with prolonged recovery beyond 6 months are not expected to recover spontaneously, indeed if paralysis persists beyond 3 months the patient will almost certainly experience residual effects (synkinesis).^{12,14} Studies exploring prognosis after facial palsy have reported that the more severe paralysis is even at 1 month, the more likely nonrecovery is.¹⁵ Following development of synkinesis improvements in a patient's condition can be attributed to appropriate specialist rehabilitation interventions as it is now understood that the lack of observed movement is due to abnormal synchronization as opposed to absent muscle activity.¹² It is important that rehabilitation is provided by specialists in facial therapy as non-specialist management may activate already overactive muscles and further reinforce abnormal patterns causing deterioration rather than improvement.¹⁶

The included patients were seen by the specialist facial therapists, who depending on the phase of recovery, treated them primarily as follows:

- (1) Acute flaccid phase: massage, ipsilateral eyelid stretching, taping, and contralateral cheek stretching.
- (2) Paretic phase: trigger point release, passive stretches, and gentle centralized movement reeducation.
- (3) Synkinetic phase: muscle release techniques, relaxation training, and neuromuscular retraining using surface electromyography feedback and synkinesis delinking exercises.

Within the synkinetic phase, those whose progress plateaued following facial therapy, were chosen for chemodenervation⁴ primarily to reduce the overactivity of ipsilateral synkinetic muscles although patients extremely bothered by contralateral hyperkinesis were injected contralaterally as required (see ►Fig. 1 for an overview of the interventions offered). In instances of late presentation to clinic post-onset, for example, patients in the synkinetic or paretic phases, their treatment started at the point of presentation. Those recalcitrant to both facial therapy and chemodenervation, were chosen for surgery in the form of selective neurolysis and myectomy.¹¹ This treatment triage system was based on clinical parameters measured by the "East Grinstead Grade of Stiffness (EGGS) scale" shown in ►Table 1. The EGGS scale is a descriptive scale which clinicians can use to support their clinical reasoning when deciding which interventions a

Table 1 The East Grinstead Grade of Stiffness (EGGS) scale used in triaging treatment options during nonflaccid facial palsy rehabilitation

EGGS	Description	Treatment required
I	Functional restoration of facial movements following specialist facial therapy alone	Long-term independent continuation of prescribed facial therapy program
II	Clinical improvement noted but plateau below level of functional restoration	Initiate chemodenervation alongside facial therapy followed by long-term independent continuation of prescribed facial therapy program
III	Ongoing stiffness and pain despite facial therapy and chemodenervation	Selective neurolysis surgery followed by long-term independent continuation of prescribed facial therapy program

patient requires to best manage their post-facial palsy sequelae.

The clinical outcomes of all patients were serially assessed by multiple assessors with physical and psychosocial outcome measures. These included the clinician-graded Facial Grading Scale (FGS) and House-Brackmann (HB) scores which were performed at clinic review appointments. Although FGS and HB scores were not always performed by an independent assessor the hospital facial palsy multidisciplinary team have been audited in completion of these measures and found to have good inter- and intrarater reliability. These measures can be used with good reproducibility by both novices and experts, and by all professionals involved in the management of facial palsy.¹⁷ Patient self-reported outcome measures (PROMs) were also used including the Facial Disability Index (FDI)¹⁸ and the Facial Clinimetric Evaluation (FaCE) scale.¹⁹ These measures are completed by the patient rather than an assessor and both have been shown to produce reliable and valid measurements¹⁷⁻¹⁹ in patients with disorders of the facial motor system.

Statistical analyses of these outcome measures were compared pre- and posttherapy between all subsets, using the two-way analysis of variance (ANOVA) test, to elicit the benefits of multimodal therapy and the effect of timing of patient presentation to therapy on patient outcomes and further treatment requirements. The chemodenervation treatment arm was analyzed using one-way ANOVA with respect to (1) interval between onset of facial therapy and chemodenervation initiation, (2) duration of chemodenervation, (3) number of botulinum toxin injections, and (4) the maximum dose given during the chemodenervation regime, while the correlation between the EGGs scale and time of presentation, represented by the four subgroups was also assessed using one-way ANOVA. Statistical significance was defined as $p < 0.05$ (GraphPad PRISM ver 8.0, USA).

Results

Of the 75 patients in this cohort, there was a female-to-male ratio of 3:1 (56 females and 19 males). The mean age within the cohort was 54 years. While there is no female preponderance in facial palsy per se, this suggests that females may be more likely to pursue facial palsy treatment. The overall mean duration of treatment was 13.9 months (group I: 10 months, group II: 13.2 months, group III: 11.1 months, group IV: 20.1 months). As regards the proportion of this cohort ($n = 75$) requiring chemodenervation as part of their multimodal therapy regime, only 56 patients required it (75% of the cohort). The subset breakdown of patients requiring chemodenervation was 92% (group I), 79% (group II), 71% (group III), and 92% (group IV).

In terms of the facial stiffness scale (EGGS), the majority of the patients were grade II requiring facial therapy and chemodenervation (71%) followed by 24% being grade I requiring facial therapy only. The mean EGGs score (1-3) for each respective group was as follows: group I: 1.5; group II: 1.76; group III: 1.77; and group IV: 2.07. One-way ANOVA proved this to be statistically significant for increased stiffness and treatment recalcitrance following delayed presentation to therapy with a p -value of 0.0016 (< 0.01). Only four patients ($n = 4$) or 5.3% of this entire cohort required surgical intervention for recalcitrant synkinesis following facial therapy \pm chemodenervation. Similarly, increasingly late clinical presentations were associated with increased durations of chemodenervation requirement ($p = 0.0016$; < 0.01), increased number of chemodenervation episodes ($p = 0.0018$; < 0.01), and increased dosage of botulinum toxin type A used per episode ($p = 0.0006$; < 0.001). However, the "time" of presentation to therapy did not significantly affect the interval between the onset of therapy and the initiation of chemodenervation ($p = 0.49$; $p = ns$). These statistics are graphically depicted in ► Fig. 2.

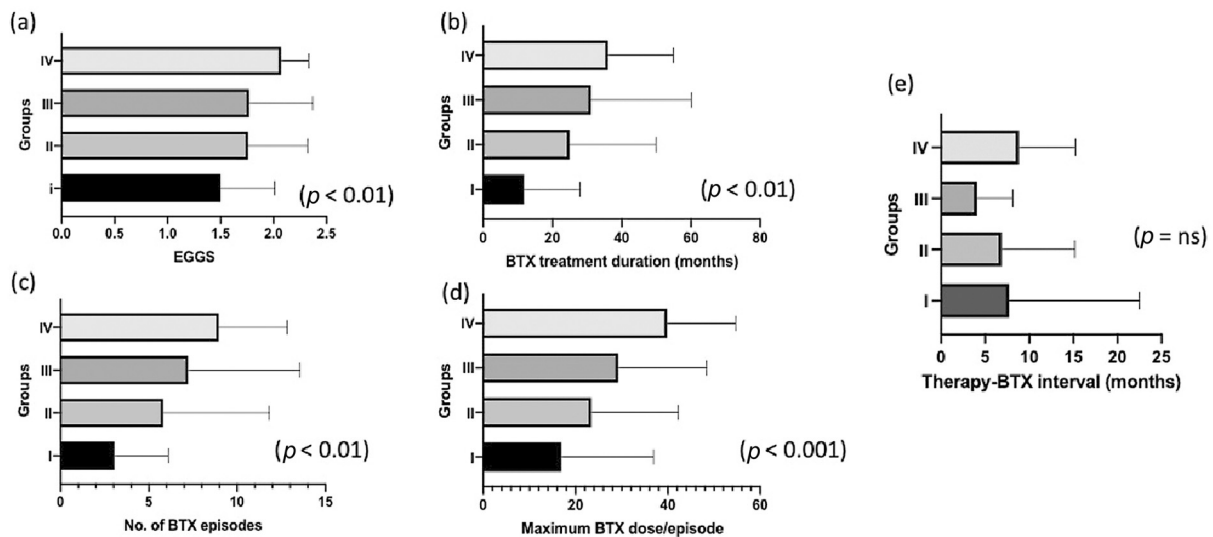
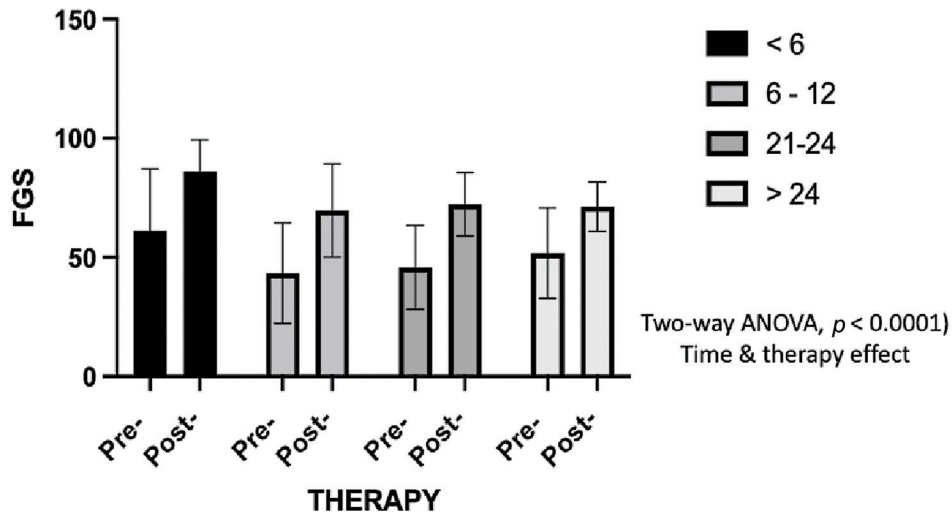


Fig. 2 (A-E) One-way analysis of variance (ANOVA) analysis of increasingly late clinical presentations showing statistically increasing. (A) East Grinstead Grade of Stiffness (EGGS) scores. (B) Duration of chemodenervation required. (C) Number of chemodenervation episodes and (D) maximum dosage of botulinum toxin type A required. (E) Interval between onset of therapy and initiation of chemodenervation.



Duration since onset	< 6 months	6 – 12 months	12 -24 months	> 24 months
Pre-therapy FGS	61.28 +/- 25.88	43.27 +/- 21.03	45.77 +/- 17.56	51.79 +/- 19.01
Post-therapy FGS	86.13 +/- 13.28	69.69 +/- 19.5	72.25 +/- 13.3	71.25 +/- 10.33

Fig. 3 In patients who started facial therapy, less than 2 years post-onset, a predictable improvement in their mean Facial Grading Scale (FGS) was noted. However, beyond 24 months, the degree of improvement is slightly reduced as depicted graphically. This is an indirect indicator that while muscle thixotropy may occur earlier on, beyond 2 years, muscle contracture may start setting in.

As shown in ►Fig. 3, overall FGS significantly improved pre- and posttherapy in all groups (mean-standard deviation, 60.13 ± 23.24 vs. 79.9 ± 13.01 ; confidence interval, -24.51 to -14.66 , $p < 0.0001$). However, this improvement slightly tapered in group IV (those presenting at more than 2 years following onset of facial palsy), indicating an increasing proportion of recalcitrant tightening in patients presenting to therapy more than 2 years after onset. Further analysis of the components of FGS (namely volitional movement, resting tone, and synkinesis), showed that multimodal therapy improved all domains of the FGS statistically significantly (see ►Figs. 4 and 5 for clinical images of patients showing

improvement after multimodal therapy.). Presenting for treatment earlier did not significantly improve volitional movement and resting tone more than late presentation ($p > 0.05$). However, early presentation rather than late presentation was significant ($p < 0.0001$) in reducing synkinesis, as shown in ►Table 2.

Patients in group I were observed to have higher volitional movement scores than late presenters, attributable to a higher proportion of these patients being in the good prognostic subcohort; those showing initial signs of recovery within 1 month post-onset with less likelihood of developing severe synkinesis.¹⁸ The mean therapy scores in late

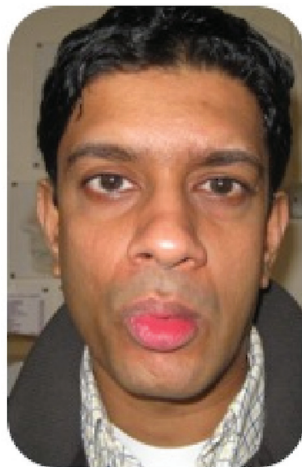
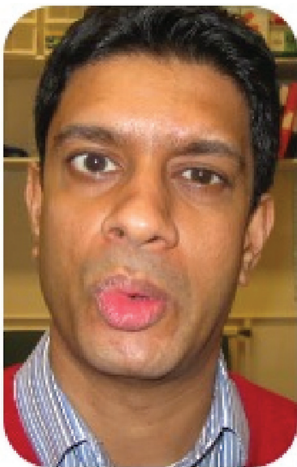


Fig. 4 Patient who presented 11 years post-onset right facial palsy due to Ramsay Hunt syndrome. Improvement in synkinesis following specialist facial therapy only.

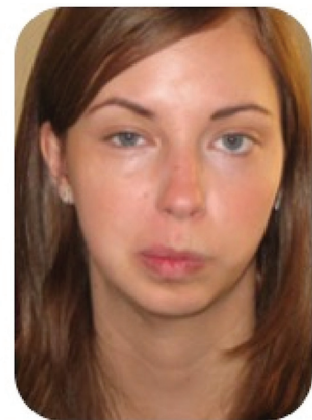
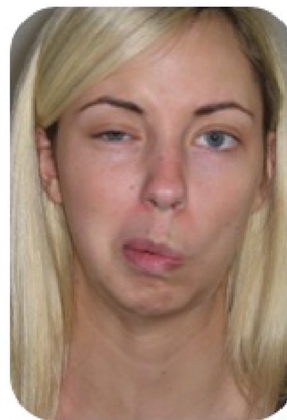


Fig. 5 Patient who presented 5 years post-onset right facial palsy following skull base fracture. Improvement in synkinesis following multimodal treatment including specialist facial therapy and chemodenervation.

Table 2 Component-wise breakdown of the effect of both time and facial therapy on the individual components of the Facial Grading Scale, using the two-way ANOVA statistical analysis (GraphPad PRISM ver 8.0)

FGS	Group	Pretherapy		Posttherapy		Statistical significance (two-way ANOVA) ^a
		Mean	SD	Mean	SD	
VM	I ^a	71.56	22.66	92	10.03	$p < 0.05$ (time effect) $p < 0.0001$ (therapy effect)
	II	60.80	18.03	78.69	15.80	
	III	65.85	12.92	81	10.42	
	IV	72.33	13.65	82.2	10.66	
RS	I ^a	9.44	5.91	3.53	2.95	$p < 0.05$ (time effect) $p < 0.0001$ (therapy effect)
	II	12	3.68	6.15	4.16	
	III	11.54	3.76	4.38	3.20	
	IV	11.25	3.69	7.5	2.57	
SS	I ^a	0.83	1.46	2.2	1.88	$p < 0.0001$ (time effect) $p < 0.0001$ (therapy effect)
	II	5.53	3.84	3.08	2.29	
	III	7.77	4.00	4.38	1.51	
	IV	8.04	2.99	3.45	1.39	

Abbreviations: ANOVA, analysis of variance; FGS, Facial Grading Scale; RS, resting symmetry; SD, standard deviation; SS, synkinesis score; VM, volitional movement.

Note: Group I (who presented within 6 months post-palsy), group II (between 6 and 12 months post-palsy), group III (between 1 and 2 years post-palsy), group IV (late presentations beyond 2 years post-palsy).

^aGroup I (good prognosticators) was excluded from statistical analyses to minimize the confounding factor of potential for natural recovery.

presenters (group IV) eventually caught up with early presenters (group I) but those in the latter group were more resistant to improvement with those in group I exhibiting more than twice the increase in volitional activity. This can likely be explained by the thixotropy effect on the facial muscles over time. Similarly, the HB index showed a significant improvement in score pre- and post-facial therapy but score improvements across groups II, III, and IV were not significantly affected by time of presentation, probably due to the relative subjectivity of the HB compared with the FGS.¹⁹

In terms of PROMs, both physical and social FDI scores were significantly improved following therapy; however, only the physical score was affected by time of presentation with early presenters (groups II and III) improving more than late presenters (group IV). There was also statistically significant improvement in the FaCE scale scores following our rehabilitation program but again improvements were not significantly affected by time of presentation to therapy (►Table 3).

Overall, the data illustrates the fact that a multidisciplinary approach is the key element in recovery. This is illustrated in ►Fig. 6, which shows statistically significant overall improvement in FGS scores before and after multimodal therapy (unpaired Student's *t*-test; $p < 0.0001$). As stated previously good prognosticators (group I), who presented within 6 months of onset, were excluded from the data analyses, given that it was a confounding factor. This is based on the fact that while 70% of patients completely recover by 6 months, the remaining 30% who have delayed recovery experience long-term sequelae which will not spontaneously improve without intervention.¹⁴ The evidence here suggests

that earlier presentation to therapy for rehabilitation can help better reduce stiffness and synkinesis long-term and that presentation to therapy at any time will significantly improve both clinician-graded and patient-reported outcomes, therefore improving patient's movement, comfort, and function.

Discussion

While the role of specialist facial therapy is being increasingly recognized as one of the cornerstones of rehabilitation following facial palsy, its early acceptance was limited by controversies regarding its efficacy. Nonspecialist physical therapy was standardly provided; including inappropriate treatment options such as gross exercises, which accounted for less successful objective outcomes. The key changes in the last decade since the Cochrane review by Teixeira et al²⁰ have been the multidisciplinary approach to facial rehabilitation and an appreciation of the importance of facial therapy being delivered by trained specialist facial therapists. There is recognition that psychosocial improvements are as important as physical improvements in facial rehabilitation.²¹ This has led to multimodal therapy,²² based on a 360-degree assessment by psychologists, facial therapists, and surgeons, followed by a step-by-step protocol as documented earlier.

In our practice, all patients are placed on a rehabilitation program starting with psychological assessment. A high CORE score may initiate psychological therapy and potentially preclude any surgical intervention until patients have completed psychological intervention. Patients must also complete facial therapy prior to being considered for any synkinesis surgery. Patients are reviewed approximately six

Table 3 Two-way ANOVA statistical analysis (GraphPad PRISM ver 8.0) of the House-Brackmann (HB), Facial Disability Index (FDI, physical and social subscores), and FaCE scoring systems, the latter two representing patient-related outcome measures (PROMs)

Score	Group	Pretherapy		Posttherapy		Statistical significance (two-way ANOVA) ^a
		Mean	SD	Mean	SD	
HB	I ^a	3.33	1.50	1.87	0.64	$p = 0.9273$ (time effect) $p < 0.0001$ (therapy effect)
	II	3.07	0.83	2.15	0.80	
	III	2.78	0.82	2.00	0.00	
	IV	2.75	0.53	2.25	0.79	
FDI-p	I ^a	67.78	21.84	91.43	13.36	$p < 0.01$ (time effect) $p < 0.0001$ (therapy effect)
	II	53.00	22.82	86.54	12.65	
	III	51.85	29.21	74.00	34.77	
	IV	61.04	24.32	81.67	11.13	
FDI-s	I ^a	65.33	23.92	85.14	16.56	$p = 0.30$ (time effect) $p < 0.0001$ (therapy effect)
	II	59.47	22.37	79.08	11.33	
	III	59.92	33.53	74.86	23.97	
	IV	57.50	18.14	74.00	17.34	
FaCE	I ^a	59.78	20.84	81.46	15.96	$p = 0.3025$ (time effect) $p < 0.0001$ (therapy effect)
	II	48.93	23.74	80.23	12.4	
	III	53.92	20.28	71	23.3	
	IV	47.63	14.43	69.95	17.31	

Abbreviations: ANOVA, analysis of variance; FaCE, Facial Clinimetric Scale; FDI-p, Facial Disability Index (physical); FDI-s, Facial Disability Index (social). Note: Group I (who presented within 6 months post-palsy), group II (between 6 and 12 months post-palsy), group III (between 1 and 2 years post-palsy), group IV (late presentations beyond 2 years post-palsy).

^aGroup I (good prognosticators) was excluded from statistical analyses to minimize the confounding factor of potential for natural recovery.

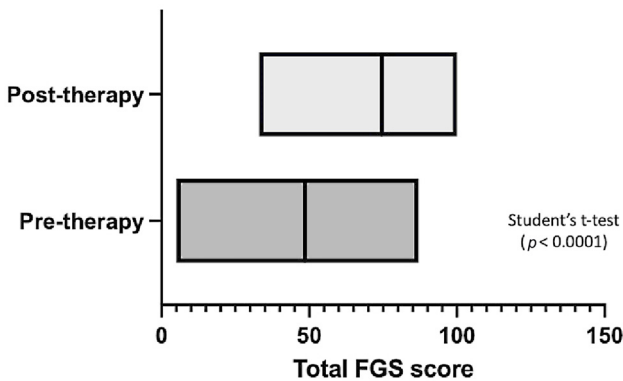


Fig. 6 Overall improvement in Facial Grading Scale (FGS) scores comparing scores pre- and postmultimodal treatment in this cohort ($p < 0.0001$).

times in therapy over the course of up to 2 years to refine their independent therapeutic skills before being discharged with the skill set to continue appropriate independent stretching, relaxation, and neuromuscular retraining for as long as required.

Using serial FGS, FDI, FaCE, and Synkinesis Associated Questionnaire scores, patients who are noted to have plateaued in term of their progress, receive tailored chemodenervation programs based on our previous experience.^{4,23} We find that low doses of botulinum toxin type A into specific synkinetic muscles, given in a distributive dose, helps relax the sarcomere units, which then allows for

greater passive lengthening of these shortened muscles by repeated stretches. This in turn affords patients an opportunity to work on coordinated movement pattern retraining while their synkinesis is minimized and muscle length is optimized. Chemodenervation treatment is tapered over time until treatment benefits plateau and the patient no longer requires intervention.

Mean improvements in overall FGS scores, plotted against advancing time scales showed that predictable increases in FGS were noted up to 24 months post-onset but beyond this period, the degree of improvement, although still substantial, tapered. Analysis of the FGS resting tone statistics between group III (12–24 months post-onset) and group IV (> 24 months post-onset), reveals a 62% improvement in resting tone scores of the former, as compared with a 33% improvement, in late presenters. This also concurs with higher EGGS scores seen among late presenters; an indicator of progressive stiffening over time which responds less well to therapeutic techniques in those that present later to therapy.

Translating this clinically, we postulate that thixotropic/shortened muscles respond better to stretching, rehabilitation, and chemodenervation in the early stages of recovery (< 2 years) but beyond this timeline, muscle fibrosis and subsequent contracture may set in, which is more resistant to therapy. Correlating this with the fact that the overall mean duration of facial therapy treatment is 13 months versus 20.1 months for those who presented beyond 2 years post-onset, it suggests that the facial muscles and function in

late presenters take comparatively longer to lengthen and improve with facial therapy/chemodeneration as well as lengthening and improving to a lesser degree.

In contrast to our experience, a study over a 20-year period from 1995 to 2016, showed no benefit from the earlier institution of facial rehabilitation but this was based purely on less specialist physiotherapy techniques.²⁴ We attribute our success in this regard, to the judicious use of highly trained specialist facial therapists and multiple treatment arms where sequential timing and therefore customized treatment, is paramount.

Moving forward, there remain questions unanswered regarding the cumulative benefits of selective neurectomies in the EGGS III patient group, which our preliminary data indicates is very effective. Histological evidence of muscle thixotropy and contracture spectrums in these patients will also deepen our understanding of facial muscle recovery following conditions like Bell's palsy. These are potential areas for future studies.

The coronavirus disease pandemic combined with increasing pressures upon NHS resources in the U.K. has encouraged us to look for innovative ways to effectively deliver our specialist facial therapy. We have therefore been working on a multidisciplinary online group training program for patients with synkinesis and will be publishing the outcomes for this group in due course. We hope that delivering our psychological therapy and specialist facial therapy in this way will continue to provide patients with the significant improvement in their physical and psychosocial outcomes that has been shown with our one-to-one therapy provision.

In conclusion, the results of this study indicate that a multimodal approach to the management of facial palsy is effective, even in those with chronically neglected synkinesis, several years post-onset. In terms of latency periods between facial palsy onset and treatment initiation, there is an advantage noted in earlier treatment, particularly as regards synkinesis reduction, until beyond 2 years post-onset when we postulate that muscle contracture begins to set in.

- Access to specialist multimodal facial rehabilitation at any time post-onset improves clinician and patient-reported outcomes even in chronic synkinesis.
- After delayed recovery early access to rehabilitation (6–24 months post-onset) results in reduced synkinesis.
- Delayed facial therapy (2 years post-onset +) may result in increased treatment recalcitrance and greater chemodeneration requirements.

Authors' Contributions

C.N.: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, visualization, writing – original draft, review and editing. T.G.: Data curation, investigation, project administration, resources. K.Y.: Data curation, investigation, project administration, resources. E.J.: Data curation, investigation, project administration, resources. R.M.: Resources, supervision, validation, writing – review and

editing. C.N.: Resources, supervision, validation, writing – review and editing. R.Y.K.: Conceptualization, formal analysis, methodology, resources, supervision, visualization, writing – review and editing.

Ethical Approval

This study adheres to the Strengthening The Reporting of OBServational Studies in Epidemiology (STROBE) guidelines, conforms to the Helsinki guidelines on ethics, and was registered with and approved by the institutional review team from the Research and Development Department at The Queen Victoria Hospital NHS Foundation Trust prior to being conducted (IRB No.1286).

Patient Consent

Patients gave their informed consent for their images to be shared.

Funding

None.

Conflict of Interest

None declared.

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