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# Varicella and isolated acute peripheral facial nerve palsy: A systematic review on natural history, prognosis and treatment

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### *Abstract*

*Background & Objective:* Varicella is a common infection during childhood and generally self-limiting. However, it can rarely cause neurological complications. Isolated acute peripheral facial palsy (APFP) is extremely rare during primary varicella infection with estimated incidence of <0.01%. There have also been conflicting opinions on its natural history, prognosis and management worldwide. We aimed to establish the natural history, prognosis and treatment for varicella-related isolated APFP in immunocompetent individuals, without co-morbids. *Methods:* Systematic review was performed with systematic literature search in Google Scholar and PubMed. Data was analysed with statistical analysis software.

Results: Thirty cases were included. The complete remission rate of APFP was 66.67% for non-treatment group and 72.22% for treatment group (p=0.643). Early and late treatment group had a similar complete remission rate of 88.89% and 80% respectively (p=1.000). However, early treatment group (within 3 days of onset) had achieved complete remission 3 weeks earlier than the late treatment group (p=0.091). Antiviral group tends to have better outcome than steroid monotherapy group, although statistically insignificant (p=0.055).

*Conclusions:* This condition generally has good prognosis even without treatment. However, early treatment and antiviral therapy may at least accelerate remission and reduce morbidities although these cannot alter the final outcome. Clinicians may consider antiviral therapy if patients present within 3 days of onset. These findings need to be applied with caution, considering the limitations of our review.

*Keywords:* Varicella, chickenpox, peripheral facial nerve palsy, facial paralysis

## INTRODUCTION

Varicella-zoster Virus (VZV) is a DNA virus under the family of Herpesviridae and also called human herpesvirus 3.[1] There are two clinically distinct forms of disease caused by VZV infection, i.e. varicella (chickenpox) and herpes zoster (shingles) infections.[2] Varicella is the primary infection of VZV, resulting in lifelong latent infection of sensory ganglia while reactivation of the latent infection results in herpes zoster.[3] Varicella is highly contagious yet generally benign and self-limiting.

During the pre-vaccine era, there were approximately 11,000 admissions for varicella (2-3 in 1000 healthy children) and 103 deaths (1 in 60,000 cases) annually in the United States.[4] After vaccine introduction, hospitalization and mortality rates declined by >70% and 88% respectively.[4]

Neurological complications from varicella are estimated to be 0.01-0.03% with cerebellar ataxia (1 in 4000 cases in unvaccinated children) and encephalitis (1 in 33,000 cases) being the commonest.[5] Other rarer neurological complications include transverse myelitis, optic neuritis, Reye syndrome, peripheral motor neuropathy, Guillain-Barre syndrome and facial nerve palsy.[5-11]

Facial nerve palsy is not an uncommon condition in the paediatric population. There have been various causes attributable to the nerve palsy, i.e. congenital, infectious, neoplastic, traumatic or idiopathic.[12-14] Causative infections include herpes simplex virus (HSV), mumps, Coxsackie

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virus, influenza, *Borrelia burgdorferi* and VZV. Almost half of the acute peripheral facial palsy (APFP) cases are due to Bell's palsy which is the appellation used to describe an APFP of unknown cause, with an incidence rate of 20-30 per 100,000 annually.[12,15] Its pathogenesis remained unknown. In 2008, Hato *et al*. postulated that Bell's palsy may be associated with reactivation of HSV in 31-79% of cases.[15] Other studies showed its association with VZV reactivation up to 37% of cases.[18-21] VZV reactivation has been demonstrated using polymerase chain reaction or serological assays in patients with zoster sine herpete and also Ramsay Hunt Syndrome (also called herpes zoster oticus).[16-20] Ramsay Hunt syndrome is characterized by a triad of ipsilateral APFP, otalgia and the presence of painful vesicular eruption in the external ear whereas zoster sine herpete is characterized by APFP in the absence of typical zoster skin lesions.[16-20]

The Copenhagen Facial Nerve study had evaluated the natural history of 2,570 cases of peripheral nerve palsy of various aetiologies over a 25-year period, including 349 children younger than 15 years old.[22] The majority of cases included were Bell's palsy (66.2%, n=1701), herpes zoster or Ramsay Hunt Syndrome (4.5%, n=116) and trauma (3.7%, n=95).[22] 6.6% cases reported in neonatal period were due to either congenital paresis or birth trauma (n=169).[22] 70% of patients with Bell's palsy (n=1189) had complete paralysis and 30% (n=512) incomplete paralysis on initial assessment.[22] Without treatment, 85% regained function within 3 weeks while the remaining 15% of patients within 3-5 months.[22] 58% achieved complete remission within 2 months. 71% had final complete remission without any sequelae, 12% had mild dysfunction (House-Brackmann Grade II), 13% moderate dysfunction (Grade III), while only 4% had moderately severe or severe dysfunction (Grade IV-V) and none remained completely paralysed.[22] Children with Bell's palsy had favourable outcome with 90% achieving complete remission while herpes zoster patients had poor outcome with only 21% regaining full function.[22] Although this study had collected a huge amount of data on peripheral facial nerve palsy of different aetiologies, as most of the studies, Peitersen *et al*. 2002 described mainly on Bell's palsy and, to a smaller extent, Ramsay Hunt syndrome.[22] In fact, none of the 2,570 cases reported were due to primary varicella infection. Again, it showed the rarity of this condition.

In our center, we treated a 2-year-old, previously well girl who was admitted for varicella infection on day 4 of illness. She had classical presentation with fever, malaise and typical vesicles in different stages with some being crusted on the trunk and left pinna but none in the external auditory canal or tympanic membrane. On day 5 of illness, she developed isolated left APFP (House-Brackmann Grade II). She was otherwise well with no other neurological deficits. She was given oral acyclovir 800mg 5 times a day for 7 days. She improved significantly after 5 days of treatment and achieved complete remission after 7 days of treatment. She remained well with no sequelae during serial clinic reviews up to 1 year after this APFP episode.

Due to the rarity of this condition, we were uncertain about the treatment effectiveness and prognosis. The natural history, management and prognosis of this clinical entity are far from well-established. They are mainly based on anecdotal experience. Hence, we performed a systematic review on acute peripheral facial nerve palsy during active varicella infection. We aimed to establish the natural history, prognosis and treatment for varicella-related isolated APFP in immunocompetent individuals, without co-morbids.

## METHODS

We have performed a systematic review using Preferred Reporting Items for Systematic Reviews and Meta-analysis of Individual Participant Data (PRISMA-IPD) guideline.

### *Search strategy*

We conducted a PubMed and Google Scholar search with a subject headings of "varicella", "chickenpox", "chicken pox", "facial palsy", "facial nerve palsy" and "facial paralysis". We reviewed publications from year 1960 to August 2019. The articles were screened and reviewed independently by two authors. We identified 7,860 records from Google Scholar and 122 from PubMed search with additional 32 records from Tanaka *et al*. (2001)[23] and Muñoz-Sellart *et al*. (2010)[24] (Figure 1).

### *Inclusion and exclusion criteria*

The inclusion criteria were case reports or case series of acute peripheral facial palsy associated with acute phase of varicella. The exclusion criteria were cases with other concurrent neurological complications such as cerebellar ataxia, cerebellitis, meningitis, encephalitis, transvers myelitis, optic neuritis and vasculopathy; cases with other concurrent cranial nerve involvement;

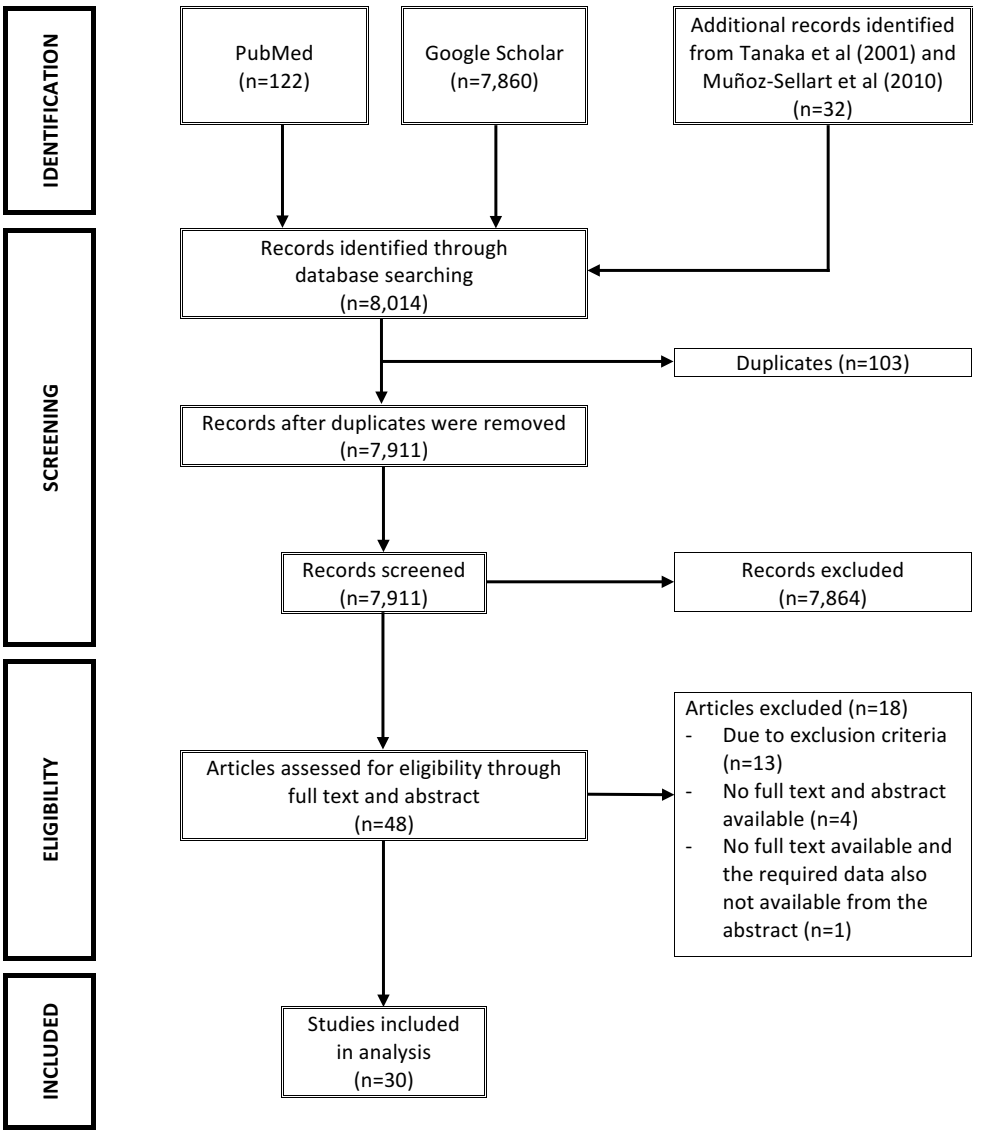


Figure 1: Showed the study search and selection using PRISMA-IPD guideline

cases with familial cause or recurrent course; Ramsay Hunt syndrome, zoster sine herpete and Guillain-Barre syndrome. We also excluded cases with immunodeficiency, immunocompromised individuals and those with other pre-existing chronic medical illness. Varicella or chickenpox was defined based on clinical diagnosis and/or serological testing while peripheral facial palsy was defined with clinical manifestation of lower motor neuron lesion of the facial nerve.

*Data collection*

After removing duplicates, screening and eligibility assessment, data were manually extracted from the text for analysis. We recorded demographics; APFP laterality, severity, onset, timing of first sign of improvement, and remission; treatment; and study duration. Data were insufficient to compare APFP severity, treatment dosages and first sign of improvement among the groups.

Early treatment was defined when the treatment was initiated within 3 days from the onset of facial palsy while it was considered as late treatment if it was initiated after 3 days. We defined complete remission as complete recovery of facial nerve function without any residual sequelae while those with residual sequelae were regarded as partial remission.

*Statistical analysis*

All the statistical analyses and calculations were conducted using IBM SPSS Statistics Version 22 (SPSS Inc., Chicago Illinois). Depending on the sample size distribution, the differences between two categorical groups were analysed using Pearson Chi-square for large sample size while Fisher's Exact Test for small sample size. With our small sample size (n=30), the differences between two scale variables were analysed using non-normally distributed method or non-parametric test, Mann Whitney U test. Non-normally distributed scale variables were presented using median and interquartile range. A significant analysis was considered as 95% confidence level or 5% level of statistical significance.

## RESULTS

We have reviewed published articles as far back as the year 1961 and identified 30 which met our criteria (Table 1). Among these, 21 were paediatrics (70%) with a median age of 5 years (range: 0.3-17 years) while 9 were adults (30%) with a median age of 26 years (range: 18-35 years). 76.7% of the cases had unilateral facial palsy, 16.6% bilateral palsy and 2 cases were not specified by the authors. Similar to the description by other authors from previous literature, we found in our review that APFP had a median onset of 7 days after chickenpox eruption, ranging from 3 days pre-eruption and 17 days post-eruption, with a median onset of 6 days post-eruption for paediatrics and 10 days post-eruption for adults. Eight cases (26.7%) were not started on any treatment while 22 cases (73.3%) were started on treatment. The demographics and clinical characteristics of the 30 cases were summarized in Table 2.

*Natural history*

Without treatment, the patients had a median remission onset of 2.36 weeks and complete remission at 4.50 weeks (median) from APFP onset. 42.86% achieved complete remission and 52.14% remained partial remission at 1 month after APFP onset. 62.50% achieved complete remission and 37.50% remained partial remission at the end of the studies with a median study duration of 1.25 months (range: 1.00-8.00 months).

From our review and postulation, those with APFP caused by chickenpox had 42.86% complete remission rate at 1 month after APFP onset; peaked with 66.67% at 2 months and remained 66.67% at 3 months after APFP.

This finding is similar to the natural history for Bell's palsy described by Peitersen *et al*. 2002 (58% achieved complete remission within 2 months).[22] Its prognosis is also much better than herpes zoster-associated APFP which had 21 % complete remission, 75% partial remission with varying severities of sequalae and 4% persistent complete loss of facial nerve function.

*Prognosis with treatment*

In the treatment (either antiviral, steroid or in combination) group, 77.27% achieved complete remission and only 22.72% had partial remission at the end of the study with a median study duration of 1 month (range: 0.50-24.00) while non-treatment group had 62.50% complete remission and 37.50% partial remission rate (p=0.643). The odd of partial remission at the end of study for those receiving treatment is 51% less likely than those without treatment (odd ratio=0.49; 95% CI=0.086-2.805) (p=0.423).

The patients in the treatment group had a complete remission rate of 61.11% at 1 month, 72.22% at 2 months and 82.35% at 3 months after APFP onset while the non-treatment group had 42.86% complete remission rate at 1 month; peaked with 66.67% at 2 months and remained 66.67% at 3 months from APFP onset.

With treatment, the patients had a median remission onset of 2.86 weeks and complete remission at 3.16 weeks (range: 1.00-11.43) from APFP onset. Those who received treatment achieved complete remission by 1.36 weeks (median) earlier than those without treatment (p=0.085). However, these were not statistically significant.

*Comparison between early treatment and late treatment*

Albeck *et al*. 1989 and Yilmaz *et al*. 2005 suggested that patients who received therapy early (≤3 days after APFP onset) responded fully while those who received treatment late (>3 days after onset) only had partial remission.[7,25] From our systematic review, those receiving therapy early (≤3 days after onset) had 85.71% complete remission while those receiving therapy late (>3 days after onset) had only 25% complete remission and 75% remained partial remission at 1 month after APFP onset (p=0.088). However, both groups had similar outcome at the end of studies (median study duration: 1.25 months) with 88.89%

**Table 1: Showed the summary of articles on varicella-associated acute peripheral facial nerve palsy (Year 1961 to 2019)**

| Study | Location of Study | Age (years) | APFP | APFP Severity | APFP Onset | Rx initiation | Antiviral | Steroid | Rx Dosage & Duration | Timing of first sign of improvement | Outcome (1 mth after onset) | Outcome (2 mths after onset) | Outcome (3 mths after onset) | Outcome (end of study) | Duration of study |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ravin (1961)[30] | US | 7 | Unilat. | NS | 14 days after varicella | NS | No | Yes | Pred dose & duration not specified | 1 mth after APFP onset | Partial remission | Partial remission | Partial remission | Partial remission (minimal residual paralysis) | 2 years |
| Charachon[31] (1971)* | France | 1 | NS | NS | 1 day before varicella | - | No | No | - | NS | NS | NS | NS | Partial remission | NS |
| Manning (1972)[32] | US | 3 | Unilat. | NS | NS | - | No | No | - | NS | Complete remission | - | - | Complete remission | 4 weeks |
| Shoji (1975)[33] | Japan | 17 | Unilat. | NS | 17 days after varicella | - | No | No | - | NS | Complete remission | Complete remission | - | Complete remission | 2 months |
| Ogino (1980)[34] | Japan | 5 | Unilat. | NS | 3 days before varicella | - | No | No | - | NS | Partial remission | Complete remission | - | Complete remission | 5 weeks |
| Muto[35] (1982)* | Japan | 11 | Unilat. | NS | 7 days after varicella | NS | No | Yes | NS | NS | Complete remission | - | - | Complete remission | 3 weeks |
| Murthy (1984)[36] | India | 22 | Unilat. | NS | 15 days after varicella | - | No | No | - | 1 mth after APFP onset | Partial remission | - | - | Partial remission | 1 month |
| Yamamoto[37] (1987)* | Japan | 27 | Bilat. | NS | Right APFP: 10 days after varicella | - | No | No | - | NS | Partial remission | Partial remission | Partial remission | Complete remission | 8 months |
| | | | | NS | Left APFP: 11 days after varicella | - | No | No | - | NS | Partial remission | Partial remission | Partial remission | Complete remission | |
| Puntous [38] (1989)** | France | 30 | Unilat. | NS | 14 days after varicella | NS | Yes | Yes | IV Acy 10mg/kg. PO Pred 1mg/kg/day. (duration not specified) | NS | Complete remission | - | - | Complete remission | 4 weeks |
| Ganjoo [39] (1989)** | India | 35 | Bilat. | NS | 1 day after varicella | NS | No | Yes | PO Pred-nisolone 60mg/day | NS | Partial remission | Partial remission | Partial remission | Partial remission | 24 weeks |
| Umemura (1991)[40] | Japan | 1.3 | Unilat. | NS | 4 days afrer varicella | 9 days after APFP onset | Yes | No | IV Acy 50mg tds for 7 days | 39 days after APFP onset | Partial remission | Partial remission | Complete remission | Complete remission | 2.6 months |

| Study | Location of Study | Age (years) | APFP | APFP Severity | APFP Onset | Rx initiation | Antiviral | Steroid | Rx Dosage & Duration | Timing of first sign of improvement | Outcome (1 mth after onset) | Outcome (2 mths after onset) | Outcome (3 mths after onset) | Outcome (end of study) | Duration of study |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bordet [41] (1992)** | France | 24 | Unilat. | NS | 10 days after varicella | NS | Yes | Yes | Acy 1.5g/day for 6 days, then 600mg/day. IV Methylpred 1g/day for 3 days, then PO Pred 1mg/kg/day for 2 months | NS | Partial remission | Partial remission | Partial remission | Partial remission | 16 weeks |
| Watanabe (1994)[26] | Japan | 6 | Unilat. | NS | 8 days after varicella | - | No | No | - | NS | Complete remission | - | - | Complete remission | 1 month |
| Van der Flier (1999)[27] | Holland | 5 | Seq. Bilat. | NS | Right APFP: 7 days before varicella | - | No | No | - | NS | Complete remission | Complete remission | Complete remission | Complete remission | 3 months |
| | | | | NS | Left APFP: 3 days after varicella | - | No | No | - | NS | Partial remission | Partial remission | Partial remission | Partial remission | |
| Ikeda [42] (1999)* | Japan | 7 | NS | NS | 11 days after varicella | NS | No | Yes | NS | NS | NS | NS | NS | Complete remission | NS |
| Tanaka (2001)[23] | Japan | 0.3 (4mth) | Unilat. | NS | 5 days after varicella | 1 day after APFP onset | Yes | No | IV Acy 40mg tds for 3 days | 30 days after APFP onset | Partial remission | Complete remission | - | Complete remission | 6 weeks |
| Deda (2002)[43] | Turkey | 2 | Unilat. | NS | 3 days after variella | 2 days after APFP onset | Yes | No | PO Acy 20mg/kg/day (4 divided doses) for 5 days. | 3 weeks after APFP | NS | NS | NS | Partial remission | 3 weeks |
| Odemis (2004)[19] | Turkey | 4 | Unilat. | HB II (onset) then became HB III 10 days after onset | 7 days after varicella | 10 days after APFP onset | Yes | Yes | PO Acy 40mg/kg/day (4 divided doses). PO Pred 2mg/kg/day for 14 days. | 18 days after APFP onset (8 days after Rx) | Complete remission 23 days after onset (14 days after Rx) | - | - | Complete remission | 1 month |
| Yilmaz (2005)[7] | Turkey | 7.5 | Unilat. | NS | 15 days after varicella | 15 days after APFP onset | Yes | No | PO Acy 20mg/kg/day (4 divided doses) for 5 days. | NS | NS | NS | NS | Complete remission | NS |
| Girija (2007)[5] | India | 31 | Unilat. | NS | 9 days after varicella | NS | Yes | No | PO Acy dose & duration not specified | NS | Complete remission | - | - | Complete remission | 1 month |

| Study | Location of Study | Age (years) | APFP | APFP Severity | APFP Onset | Rx initiation | Antiviral | Steroid | Rx Dosage & Duration | Timing of first sign of improvement | Outcome (1 mth after onset) | Outcome (2 mths after onset) | Outcome (3 mths after onset) | Outcome (end of study) | Duration of study |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rama (2008)[8] | India | 26 | Unilat. | NS | 10 days after varicella | NS | Yes | Yes | PO Acy 800mg 5x/day for 7 days. PO Pred 10mg tds (in tapering dose for 3 weeks). | NS | Complete remission | - | - | Complete remission | 3 weeks |
| Ikemiyagi (2008)[29] | Japan | 5 | Unilat. | Yana 20/40 | 7 days after varicella | 7 days after APFP onset | Yes | Yes | PO Acy 80mg/kg/day. IV Hydrocort (dose: NS) (total steroid 6 wk). | 20 days after APFP onset | Partial remission | Complete remission | - | Complete remission | 6 weeks |
| Al-Abadi (2010)[44] | UK | 8 | Bilat. | NS | A few days after varicella | NS | Yes | No | PO Valacy for 5 days (dose: NS). | NS | Complete remission | - | - | Complete remission | 1 month |
| Ferreira (2014)[9] | Portugal | 15 | Unilat. | NS | 11 days after varicella | 3 days after APFP onset | Yes | No | PO Acy 80mg/kg/day (4 divided doses) for 5 days. | 8 days after onset (5 days after Rx) | NS | NS | NS | Complete remission | NS |
| Oghan (2017)[10] | Turkey | 4 | Unilat. | HB II | A few days after varicella | 2 days after APFP onset | Yes | Yes | IV Acy 30mg/kg/day for 5 days, followed by PO Valacy for 14 days. PO Pred 1mg/kg/day. | 7 days after onset (5 days after Rx) | Complete remission | - | - | Complete remission | 1 month |
| Bains (2017)[45] | India | 18 | Unilat. | NS | 4 days after varicella | 3 days after APFP onset | Yes | Yes | PO Valacy 1g TDS. Methylpred 8g BD. (duration not specified) | NS | Complete remission (10 days after Rx) | - | - | Complete remission | 2 weeks |
| Hanalioglu (2018)[11] | Turkey | 12 | Unilat. | NS | 3 days after varicella | 4 days after APFP onset | No | Yes | PO Pred 50mg OD for 3 days, then reduced by 10mg every 3 days (total 15 days). | NS | Partial remission | Partial remission | - | Partial remission | 2 month |
| Petković (2018)[46] | Croatia | 3 | Unilat. | NS | 4 days after varicella | NS | Yes | Yes | IV Acy 10mg/kg tds for 7 days. PO Pred 1mg/kg OD tapering over 2 weeks. | NS | Complete remission | - | - | Complete remission | 3 weeks |

| Study | Location of Study | Age (years) | APFP | APFP Severity | APFP Onset | Rx initiation | Antiviral | Steroid | Rx Dosage & Duration | Timing of first sign of improvement | Outcome (1 mth after onset) | Outcome (2 mths after onset) | Outcome (3 mths after onset) | Outcome (end of study) | Duration of study |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Chatterje (2019)[47] | India | 19 | Bilat. | NS | 5 days after varicella | 2 days after APFP onset | Yes | Yes | PO Acy 4000mg every day for 14 days. PO Pred 60mg OD for 14 days. | NS | Complete remission | - | - | Complete remission | 2 weeks |
| Teng (2019) *Index case Unpublished* | Malaysia | 2 | Unilat. | HB II | 4 days after varicella | 1 day after APFP onset | Yes | No | PO Acy 800mg 5x/day for 7 days. | 5 days after onset | Complete remission (7 days after Rx) | Complete remission | Complete remission | Complete remission | 2 years |

**Abbreviations**
APFP, Acute peripheral facial nerve palsy; Rx, Treatment; Mth(s), Month(s); Wk(s), Week(s); Unilat., Unilateral; Bilat., Bilateral; Seq. Bilat., Sequential Bilateral; NS, Not specified or unknown; IV, Intravenous; PO, oral; Acy, Acyclovir; Valacy, Valacyclovir; Pred, Prednisolone; Hydrocort, Hydrocortisone; Methylpred, Methylprednisolone; HB II, House-Brackmann Classification grade II; HB III, House-Brackmann Classification grade III; Yana 20/40, Yanagihara Facial Nerve Grading system score 20/40
" _ ": not given or not applicable
*The data was extracted from Tanaka et al 2001.23
**The data was extracted from Muñoz-Sellart et al 2010.

complete remission from early treatment group and 80% from late treatment group (p=1.000).

Although statistically insignificant, early treatment group tends to have earlier complete remission (median 3.0 weeks earlier) than late treatment group (p=0.091). The early treatment group achieved complete remission at median 2.00 weeks (range: 1.00-6.00 weeks) from APFP onset while the late treatment group at median 6.00 weeks (range: 3.29-11.43 weeks).

*Comparison between treatment options*

Eight cases were (36.4%) started on antiviral monotherapy, 5 cases (22.7%) on steroid monotherapy and 9 (40.9%) on combination therapy (antiviral+steroid). Those who received antiviral monotherapy had a median interval of 5 days between varicella and APFP onset; those with antiviral-steroid combination therapy 7 days; and those with steroid monotherapy had the longest median interval of 9 days. Treatment were initiated at a median of 2.5 days (range: 1-15 days) after the APFP onset with a median study duration of 1.13 months (range: 0.5-24 months) stating the patient outcome. We analysed the outcomes at the end of studies among the use of antiviral, systemic glucocorticoid and its combination:

(a) Antiviral therapy vs steroid monotherapy

The antiviral group (antiviral monotherapy and antiviral-steroid combination therapy) tends to have better outcome than steroid monotherapy at the end of studies with p value barely <0.05. The antiviral group had 88.24% complete remission while the steroid monotherapy group had only 40% complete remission. (p=0.055).

Among the steroid monotherapy group (n=5), only 1 case developed APFP early during chickenpox infection (within first week) but the timing of initiation of steroid therapy was not specified. The remaining cases either developed APFP later during chickenpox infection (after 1 week of onset) or received steroid 1 week after varicella onset.

(b) Antiviral monotherapy vs steroid monotherapy

The antiviral monotherapy group had 87.5% complete remission while the steroid monotherapy group had only 40% complete remission. However, it was not statistically significant. (p=0.217).

**Table 2: Showed the summary of the demographics and clinical characteristics of the 30 published articles included in our systematic review**

| Demographics & Clinical Characteristics | n (%) | Median (range) |
|---|---|---|
| Adult | 9 (30%) | - |
| Paediatrics | 21 (70%) | - |
| Age (in years) | | 7.25 (0.3 - 35) |
| Unilateral facial nerve palsy | 23 (76.7%) | - |
| Bilateral facial nerve palsy | 5 (16.6%) | - |
| Not specified | 2 (6.7%) | - |
| Facial palsy onset (days from varicella eruption) (n=27) | | 7 (-3 - 17) |
| No treatment | 8 (26.7%) | - |
| Treatment | 22 (73.3%) | - |
| Antiviral monotherapy | 8 (36.4%) | - |
| Antiviral-steroid combination therapy | 9 (40.9%) | - |
| Steroid monotherapy | 5 (22.7%) | - |
| Early treatment (within 3 days from facial palsy onset) | 9 (64.3%) | - |
| Late treatment (after 3 days from facial palsy onset) | 5 (35.7%) | - |
| Treatment initiation (days from facial palsy onset) (n=14) | | 2.5 (1 - 15) |
| Study duration (in months) (n=26) | | 1.13 (0.5 - 24) |

(c) Antiviral-steroid combination therapy vs steroid monotherapy
Those receiving antiviral-steroid combination therapy had 88.89% complete remission while steroid monotherapy had 40% complete remission at the end of studies with a p value of 0.095.

(d) Antiviral monotherapy vs antiviral-steroid combination therapy
There was no statistically significant difference in complete remission at the end of studies between these 2 groups with the former having 87.5% complete remission and the latter 88.89% (p=1.000). Those receiving antiviral monotherapy started to recover at 3.00 weeks from APFP onset and achieved complete remission at 4.00 weeks while those receiving antiviral-steroid combination therapy had recovery at 2.57 weeks (p=0.456) and achieved complete remission at 3.15 weeks (p=0.825).

## DISCUSSION

Watanabe *et al*. described that facial nerve palsy can appear 5 days before and 16 days after chickenpox eruption.[11,26] Watanabe *et al*. also hypothesized haematogenous spread of infection for those with pre-eruptive onset of APFP and neurogenous route for those with post-eruptive onset.[26] As described by previous studies, we postulated in our patient that the VZV from the pinna vesicles may have invaded the facial nerve sensory branches and then to adjacent motor branches, causing nerve injury by either direct viral invasion or immunologically mediated inflammatory responses.[9,11] The hypothesized pathogenesis has been quite consistent throughout the years, whereas the natural history, prognosis and treatment for this clinical entity has been so far contradicting. In 1999, van der Flier *et al*. described that 50% of cases recovered completely within 1 month and their recovery was independent of the therapy prescribed.[27] On the other hand, due to limited literature available, some extrapolated its prognosis and management from large scale studies of Bell's palsy, stating high spontaneous recovery rate. However, some other authors extrapolated from studies of Herpes zoster-related APFP that this index clinical entity had poorer prognosis and early treatment should be given.[19,28] Just as described by Peitersen[22], the prognosis of individual cases of facial nerve palsy, with or without treatment, varies with aetiologies.[12] We should be cautious as the APFP in our context is associated with primary VZV infection, i.e. varicella.

From our review, we found that acute

peripheral facial palsy occurring at the time of primary chickenpox infection generally had good prognosis with 66.67% complete remission 2 months after its onset even without treatment. There was no statistically significant difference in the complete remission rate between treatment and non-treatment groups (p=0.643). Similarly, there was no statistically significant difference in the rate of complete remission between the early and late treatment group. However, early treatment group tends to achieve complete remission earlier (median 3.0 weeks earlier) than late treatment group, although statistically insignificant (p=0.091). Early treatment could potentially accelerate recovery and reduce morbidities even if it could not alter the final outcome. Among the treatment options, we found that the antiviral group (antiviral monotherapy and antiviral-steroid combination therapy) tends to have better outcome than steroid monotherapy group at the end of studies with p value barely <0.05.

We also made assumptions that the statistical significance of the superiority with early treatment over late treatment and the use of either antiviral monotherapy or antiviral-steroid combination therapy over steroid monotherapy was likely limited to a certain extent by the small available sample size of our review.

As stated above, our systematic review has some important limitations. Firstly, due to its rarity, the sample size is too small. Secondly, quite a number of previous reports had only a brief summary of the case, overlooking certain important information, including facial palsy severity. Among the 30 reports from our review, there were only 4 articles (13%) objectively stating the severity of APFP using well-recognised classification systems, i.e. House-Brackmann classification[10,19] and Yanagihara Facial Nerve Grading System.[29] We think the palsy severity is particularly important as it is potentially one of the main outcome predictors. Other potential factors influencing the prognosis were not adequately documented including treatment dosage, treatment duration and the timing of the first sign of recovery. Thirdly, in most reports, the patients were only studied for a short duration with a median of 1.13 months. This is particularly true for those with partial remission who should be studied for a longer period to determine the rate and extent of recovery at different points of time.

Considering the limitations of our review, we should be cautious when interpreting the findings. Future case reports should include all of the following information to facilitate review articles of better quality: 1. Age of the patient; 2. Facial palsy laterality (unilateral/bilateral); 3. Facial palsy severity classification (e.g. House-Brackmann Classification); 4. Facial palsy onset in relation to varicella infection; 5. Interval between treatment initiation and facial palsy onset; 6. Treatment dosage and duration; 7. Timing of first sign of improvement; 8. Longer period of study (e.g. up to 1 year after onset) especially for those with incomplete remission; 9. Serial extent of recovery documented at each review. More frequent review for the first 3-4 months after facial palsy (e.g. 1 month, 2 month, 3 month after onset, etc); 10. Objectively specify the severity of residual facial nerve dysfunction if no complete remission at the end of study (using tools e.g. House-Brackmann Classification).

In conclusion, our review showed that APFP caused by varicella had similar prognosis as Bell's palsy but significantly better prognosis than herpes zoster-associated APFP. It generally has good prognosis even without treatment. However, clinicians may consider using antiviral with or without steroid therapy during early course of the disease (within 3 days of onset) as early treatment may accelerate remission. Nevertheless, our findings need to be interpreted or applied with caution considering the limitations of our systematic review. Important and standardized information are required in future case reports to facilitate systematic review of better quality for guideline development.

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## DISCLOSURE

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