# 1. Evidenztabellen Leitlinie Optikusneuritis

## Inhaltsverzeichnis

# 1 Evidenztabellen

## 1.1 Aggregierte Evidenz

### a) Leitlinien

| Quelle | Empfehlungen & Abschnittangaben/ Nummerierung | Evidenz- und Empfehlungs-grad | Literaturbelege | Bemerkungen | Methodische Bewertung |
|---|---|---|---|---|---|
| | | | | | |
| [1] Sellner, J., et al., *EFNS guidelines on diagnosis and management of neuromyelitis optica.* Eur J Neurol, 2010. **17**(8): p. 1019-32 ((81)) | 8-10 Therapie der *atypischen* Optikusneuritis | 3 | Sellner, J., et al., EFNS guidelines on diagnosis and management of neuromyelitis optica. Eur J Neurol, 2010 | « SEARCH STRATEGY: Evidence for this guideline was collected by searches for original articles, case reports and meta-analyses in the MEDLINE and Cochrane databases. In addition, clinical practice guidelines of professional neurological and rheumatological organizations were studied. ... Due to lack of studies fulfilling requirement for the highest levels of evidence, the task force suggests | DELBI 1.0 [2]<br>Domäne 3 : durchschnittlich 3 Punkte<br><br>Domäne 6 : durchschnittlich 4 Punkte |

| Quelle | Empfehlungen & Abschnittangaben/ Nummerierung | Evidenz- und Empfehlungs-grad | Literaturbelege | Bemerkungen | Methodische Bewertung |
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| | | | | concepts for treatment of acute exacerbations and attack prevention based on expert opinion. | |

## b) Systematischer Review, Metaanalyse, HTA

| Studien-typ | Quelle | Untersuchte Studien | (verglichene) Interventionen/ (ggf. Dosierung) | Ergebnisse | Methodische Bemerkungen | Literaturbelege | Evidenzniveau (SIGN)[3] |
|---|---|---|---|---|---|---|---|
| SR | [4] Toosy, A.T., D.F. Mason, and D.H. Miller, Optic neuritis. Lancet Neurol, 2014. 13(1): p. 83-99 ((1)) | Literatur-suche Pubmed 1970-2013, general search term “optic neuritis” + “optical coherence tomography”, “cortico steroid”, “plasma-pheresis”, “magnetic resonance imaging”. English or languages if referenced in a selected English article ; preferentially articles not older than 10 years | Dosis and treatment of typical and atypical optic neuritis | Corticosteroids:<br>1.acute relapse :<br>intravenous dose<br>Followed by<br>2. 0·75–1 mg/kg per day orally tapered slowly over 6 months.<br><br>Azathioprine :<br>maintenance dose 2·5–3·0 mg/kg per day<br><br>Mycophenolate :<br>500 mg daily, increasing every week in 500 mg steps to a maintenance dose of 1 g twice daily.<br><br>Methotrexate :<br>maintenance dose 15 mg/week, starting at 7·5 mg/ week<br><br>Rituximab :<br>1 g iv days 1 and 14, repeated every 6 months | Literatursuche Pubmed 1970-2013<br>Methodische Schwächen :<br>- ausschliesslich englische Publikationen oder solche, die in engl. Publikationen zitiert wurden<br>keine Informationen über Kriterien zum Verwerfen von Literaturstellen | [4] | 3 |

| Studien-typ | Quelle | Untersuchte Studien | (verglichene) Interventionen/ (ggf. Dosierung) | Ergebnisse | Methodische Bemerkungen | Literaturbelege | Evidenzniveau (SIGN)[3] |
|---|---|---|---|---|---|---|---|
| | | | | ( | | | |
| SR | [5] Britze, J., G. Pihl-Jensen, and J.L. Frederiksen, *Retinal ganglion cell analysis in multiple sclerosis and optic neuritis: a systematic review and meta-analysis.* J Neurol, 2017. ((57)) | Peer-reviewed studies published prior to April 2016 were searched using PubMed, EMBASE, Web of Science and Scopus | Meta-analysis compared GCL thickness in MS patients with and without prior ON to healthy controls. | In acute ON, studies showed significant thinning of the GCL within the first 5 weeks (n = 5), earlier than retinal nerve fibre layer (RNFL) thinning. GCL thinning at 1-2 months after acute ON predicted visual function at 6 months (n = 3). The meta-analysis showed that the thickness of the GCL was significantly reduced in MS patients both with and without previous ON compared to healthy controls. GCL thinning was associated with visual function in most studies (n = 10) and expanded disability status scale (EDSS) scores (n = 6). In acute ON, thinning of the GCL is measurable prior to RNFL thinning, and GCL thickness | « 42/252 studies were reviewed » : keine Informationen über Kriterien zum Verwerfen von Literaturstellen | [5] | 1 |

| Studien-typ | Quelle | Untersuchte Studien | (verglichene) Interventionen/ (ggf. Dosierung) | Ergebnisse | Methodische Bemerkungen | Literaturbelege | Evidenzniveau (SIGN)[3] |
|---|---|---|---|---|---|---|---|
| | | | | after 1-2 months may predict visual function after 6 months | | | |
| SR | Gal, R.L., S.S. Vedula, and R. Beck, *Corticosteroids for treating optic neuritis.* Cochrane Database Syst Rev, 2012. 4: p. CD001430 ((108)) | Included : randomized trials that evaluated corticosteroids, in any form, dose or route of administration, in people with acute optic neuritis ; included six randomized trials | To assess the effects of corticosteroids (intravenous, oral) compared to placebo on visual recovery of patients with acute optic neuritis | In a meta-analysis of trials evaluating corticosteroids with total dose greater than 3000 mg administered intravenously, the relative risk of normal visual acuity with intravenous corticosteroids compared with placebo was 1.06 (95% confidence interval (CI) 0.89 to 1.27) at six months and 1.06 (95% CI 0.92 to 1.22) at one year. The risk ratio of normal contrast sensitivity for the same comparison was 1.10 (95% CI 0.92 to 1.32) at six months follow up. We did not conduct a meta-analysis for this outcome at one year follow up since there was substantial | SEARCH METHODS: CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2012, Issue 1), MEDLINE (January 1950 to February 2012), EMBASE (January 1980 to February 2012), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to February 2012), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en); no date or language restrictions. Two authors independently extracted the data on methodological quality and outcomes for analysis | [6] | 1 |

| Studien-typ | Quelle | Untersuchte Studien | (verglichene) Interventionen/ (ggf. Dosierung) | Ergebnisse | Methodische Bemerkungen | Literaturbelege | Evidenzniveau (SIGN)[3] |
|---|---|---|---|---|---|---|---|
| | | | | statistical heterogeneity. The risk ratio of normal visual field for this comparison was 1.08 (95% CI 0.96 to 1.22) at six months and 1.02 (95% CI 0.86 to 1.20) at one year | | | |

## 1.2 Einzelstudien

| Quelle/ Studientyp<br><br>((X)) Lit.stelle in der LL | Population (ka= keine Angabe) | (verglichene) Interventionen/ ggf. Dosierung/ ggf. Follow-up | Outcomes (Primäre und sekundäre Endpunkte ) | Ergebnisse | Bemerkungen | Evidenzniveau (SIGN) |
|---|---|---|---|---|---|---|
| [7] Optic Neuritis StudyGroup, The clinical profile of optic neuritis. Experience of the Optic Neuritis Treatment Trial. Optic Neuritis Study Group. Arch Ophthalmol, 1991. 109(12): p. 1673-8<br>- Clinical, | 448 patients entered into the Optic Neuritis Treatment Trial : 77.2% women, mean age 31.8 years. | Description of clinical profile of acute optic neuritis | Primary outcome : pain + visual loss secondary outcome : papilledema | Pain accompanied visual loss in 92.2% ,optic disc swollen in 35.3%, normal in 64.7%, MRI : demyelination 48.7%.<br>MRI, serology, roentgenography, lumbar puncture : limited utility in defining a cause for visual loss other than optic neuritis associated with demyelinative disease. | Methodische Schwächen :<br><br>- ausschliesslich englische Publikationen oder solche, die in engl. Publikationen zitiert wurden<br><br>- keine Informationen über Kriterien zum Verwerfen von Literaturstellen | 3 |

| Quelle/ Studientyp ((X)) Lit.stelle in der LL | Population (ka= keine Angabe) | (verglichene) Interventionen/ ggf. Dosierung/ ggf. Follow-up | Outcomes (Primäre und sekundäre Endpunkte ) | Ergebnisse | Bemerkungen | Evidenzniveau (SIGN) |
|---|---|---|---|---|---|---|
| - Multicenter,<br>- Randomized,<br>- Controlled<br>- Trial ((19)) | | | | | | |
| [8] Sellebjerg, F., et al., *A randomized, controlled trial of oral high-dose methylprednisolone in acute optic neuritis.* Neurology, 1999. **52**(7): p. 1479-84 ((106)) | Dänemark 1993-7<br>Alter 18-55<br>60% Frauen in der behandelten, 63% Frauen in der Kontrollgruppe | Treatment: Methylprednisolone tablets 500 mg once daily for 5 days, followed by 400, 300, 200, 100, 64, 48, 32, 16, 8 and 8 mg on each of the 10 following days<br>Control: Identical looking tablets for 15 days (not explicitly stated) | Visual acuity (Snellen)<br>Visual field not measured systematically<br>Contrast sensitivity | VAS score (p = 0.008) but not the spatial visual function (p = 0.03) differed in methylprednisolone- and placebo-treated patients during the first 3 weeks. After 8 weeks : comparable improvement in VAS scores (p = 0.8) and spatial visual function (p = 0.5) with methylprednisolone- and placebo. A post hoc subgroup analysis :patients with more severe baseline visual deficit and patients treated early after onset had a more pronounced response to treatment. The risk of a new attack within 1 year was unaffected by treatment. No serious | Method of randomization: Random number table; randomized in blocks of 10 using random numbers table and stratified as visual acuity < 0.1 and visual acuity of at least 0.1<br>Number randomized: 60, 30 to treatment; 30 to control<br>Exclusions after randomization: No exclusions<br>Losses to follow up: 5 in treatment group (1 patient after eight weeks and 4 after one year); 4 in control group at one year<br>Method of allocation concealment: Numbered sealed envelopes, unopened by investigators until all patients completed the trial<br>Participant masking: Yes<br>Provider masking: Yes<br>Outcome assessor masking: Yes<br>Intention to treat analysis: No | 1 |

| Quelle/ Studientyp<br><br>((X))<br>Lit.stelle in der LL | Population<br>(ka= keine Angabe) | (verglichene) Interventionen/ ggf. Dosierung/ ggf. Follow-up | Outcomes<br>(Primäre und sekundäre Endpunkte ) | Ergebnisse | Bemerkungen | Evidenzniveau (SIGN) |
|---|---|---|---|---|---|---|
| | | | | adverse events were seen. | | |
| [9] Wakakura, M., et al., *Multicenter clinical trial for evaluating methylprednisolone pulse treatment of idiopathic optic neuritis in Japan. Optic Neuritis Treatment Trial Multicenter Cooperative Research Group (ONMRG).* Jpn J Ophthalmol, 1999. 43(2): | Country and period of study: 22 centers in Japan (March 1991 to December 1996)<br>Age: 14 to 58 (Mean 36.3 years)<br>Sex: Overall, 69% were female | Treatment: Intravenous methylprednisolone (1 g/d) for 3 days followed by oral corticosteroid for 7 to 10 days. Intravenous administration was carried out over 45 to 60 minutes once a day in the morning<br>Control: Intravenous mecobalamin (500 ug/d) for 3 days, followed by oral mecobalamin for at least 7 days. Intravenous administration was carried out over 45 to 60 minutes once a | Visual acuity (Measured using Landolt rings at 5 m after full refractive correction. Results expressed as decimal activity)<br>Visual field ( Contrast sensitivity (Visual Contrast Test System at a testing distance of 1 m) | | Method of randomization: “Randomly assigned by the envelope method”<br>Number randomized: 102<br>Exclusions after randomization (total and per group): 32 dismissed after start of study due to different reasons including misdiagnosis and lost data. 2 patients excluded before treatment, 2 more during treatment due to waiver of consent by the patients. (Final: 66 - 33 Treatment, 33 Control groups).<br>Exclusions per group not explicitly stated<br>Losses to follow up: No loss to follow up<br>Method of allocation concealment: Serially numbered in sealed opaque envelopes<br>Participant masking: Yes<br>Provider masking: No (attending physician was informed of the intervention)<br>Outcome assessor masking: Yes<br>Intention to treat analysis: No | 1 |

| Quelle/ Studientyp ((X)) Lit.stelle in der LL | Population (ka= keine Angabe) | (verglichene) Interventionen/ ggf. Dosierung/ ggf. Follow-up | Outcomes (Primäre und sekundäre Endpunkte ) | Ergebnisse | Bemerkungen | Evidenzniveau (SIGN) |
|---|---|---|---|---|---|---|
| p. 133-8 ((107)) | | day in the morning | | | | |
| [10] Beck, R.W., et al., *A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. The Optic Neuritis Study Group.* N Engl J Med, 1992. 326(9): p. 581-8. ((23)) | Method of randomization: Randomized using permuted block design, stratified by clinical center<br>Losses to follow up: 17 at 6 months.<br>Method of allocation concealment: Bottles with pills prepared at a central location with a numbered envelope-type sealed label. Intact label was verified on return of the same to the central area<br>Participant masking: Yes except for IV group | Treatment 1: Intravenous methylprednisolone 250 mg every 6 hrs for 3 days followed by 1 mg/kg body weight of oral prednisone for 11 days<br>Treatment 2: Oral prednisone 1mg/kg/day for 14 days, tapered with administration of 20 mg on day 15 and 10 mg on days 16 and 18<br>Control: Oral placebo 1 mg/kg/day for 14 days with similar treatment as oral corticosteroid group on days 15, 16 and 18 | Visual acuity (Retro illuminated Snellen ETDRS chart)<br>Visual field (Humphrey Visual Field Analyzer and Goldmann perimeter)<br>Contrast sensitivity (Pelli-Robson chart)<br>Quality of life: Assessed using National Eye Institute Visual Function Questionnaire (NEI-VFQ) - administered 5 to 8 years after acute optic neuritis, again at 10 to 12 | 1. Visual function recovered faster in the group receiving intravenous methylprednisolone than in the placebo group; this was particularly true for the reversal of visual-field defects (P = 0.0001). Although the differences between the groups decreased with time, at six months the group that received intravenous methylprednisolone still had slightly better visual fields (P = 0.054), contrast sensitivity (P = 0.026), and color vision (P = 0.033) but not better visual acuity (P = 0.66)<br>2. Visual outcome in the oral-prednisone group did not differ from that in the placebo group.<br>3. Rate of new episodes of optic neuritis was higher in the group receiving oral | Randomisierung : a permuted-blocks design with a separate sequence for each clinical center was used to assign patients randomly in equal numbers to three treatment groups<br>Fallzahlplanung : 145 Patienten pro Gruppe, Power 0,8<br><br>Stratifizierung entspr. Ausgangsvisus<br>The distributions of the data on visual function in each group at six months were compared by a univariate Wilcoxon rank-sum test, and all four measures were combined for the Wei—Lachin test of stochastic ordering.<br>The relative risk that each measure would demonstrate recovery of function to normal was calculated from the cumulative incidence of return to normal within the six-month follow-up period with the Mantel Haenszel method.<br>The rate of recovery was analyzed for the entire six months by life-table analysis with the Kruskal—Wallis test | 1 |

| Quelle/ Studientyp<br><br>((X))<br>Lit.stelle in der LL | Population<br>(ka= keine Angabe) | (verglichene) Interventionen/ ggf. Dosierung/ ggf. Follow-up | Outcomes<br>(Primäre und sekundäre Endpunkte ) | Ergebnisse | Bemerkungen | Evidenzniveau (SIGN) |
|---|---|---|---|---|---|---|
| | Provider masking: Yes except for IV group<br>Outcome assessor masking: Not for IV group. Only 6 % of testing in both the oral treatment arms at 6 months was performed by an individual who randomized the patient.<br>Intention to treat analysis: Yes<br>Country and period of study: 15 centers in USA (July 1988 to June 1991)<br>Age: 18 to 46, (mean 32 years)<br>Sex:77% female<br>Patientenzahl (n = 457 )<br>Nach Randomisierung | Adherence: All but 14 patients (3%) completed their course of treatment. Compliance was evaluated via comparison of the number of pills in each bottle returned to study headquarters, with the number expected from that participant<br><br>patients with acute optic neuritis to receive oral prednisone (1 mg per kilogram of body weight per day) for 14 days; intravenous methylprednisolone (1 g per day) | years, and again at 15 to 18 years after acute optic neuritis | prednisone, but not the group receiving intravenous methylprednisolone, than in the placebo group (relative risk for oral prednisone vs. placebo, 1.79; 95 percent confidence interval, 1.08 to 2.95)<br>Baseline visual acuity was the best predictor of the 6-month visual acuity outcome (P = 0.0001) | for censored data.<br>The treatment groups were compared in terms of the side effects of medication by the chi-square test of association in contingency tables, and in terms of weight gain by analysis of variance with two contrasts (each steroid group vs. the placebo group)<br>Using all our follow-up data (follow-up, 6 to 24 months for each patient), differences between the groups in the rate of new episodes of optic neuritis and the rate of development of multiple sclerosis were analyzed by Kaplan–Meier product-limit method with a Mantel log-rank test, and relative risks were calculated by proportional-hazards analysis | |

| Quelle/ Studientyp<br><br>((X)) Lit.stelle in der LL | Population<br>(ka= keine Angabe) | (verglichene) Interventionen/ ggf. Dosierung/ ggf. Follow-up | Outcomes<br>(Primäre und sekundäre Endpunkte ) | Ergebnisse | Bemerkungen | Evidenzniveau (SIGN) |
|---|---|---|---|---|---|---|
| | wurden 4 Patienten ausgeschlossen (2 : compressive optic neuropathy rather than optic neuritis;2 other patients who did have optic neuritis were found to have connective-tissue diseases)<br><br>Clinical, comparative, randomized controlled trial : permuted- blocks design was used to assign patients randomly in equal numbers to 3 treatment groups<br>Einschluss-kriterien :<br>18-46 Jahre<br>Symptome, die mit akuter einseitiger | for 3 days, followed by oral prednisone (1 mg per kilogram per day) for 11 days; or oral placebo for 14 days<br>6 Monate follow-up | | | | |

| Quelle/ Studientyp<br><br>((X)) Lit.stelle in der LL | Population<br>(ka= keine Angabe) | (verglichene) Interventionen/ ggf. Dosierung/ ggf. Follow-up | Outcomes<br>(Primäre und sekundäre Endpunkte ) | Ergebnisse | Bemerkungen | Evidenzniveau (SIGN) |
|---|---|---|---|---|---|---|
| | Optikusneuritis mit Sehbeeinträchti-gung von mind. 8 Tagen Dauer vereinbar ist + relativer afferenter Pupillendefekt+ Gesichtsfeldaus-fall im betroffenen Auge | | | | | |

# 2 Abkürzungsverzeichnis

| Abkürzung | Erläuterung (ggf. deutsche Übersetzung) |
|---|---|
| VAS | Visual acuity score |
| MRI | Magnetic resonance imaging |
| GCL | Ganglion cell layer |
| iv | intravenous |
| ON | Optic neuritis |
| SIGN | Scottish Intercollegiate Guidelines Network, Cochrane Risk of Bias Tool |

Die Nummer der Publikation in der Leitlinie ist in einer Doppelklammer ((x))) aufgeführt.

# 3 Literatur

1. Sellner, J., et al., *EFNS guidelines on diagnosis and management of neuromyelitis optica.* Eur J Neurol, 2010. 17(8): p. 1019-32.
2. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften , Ä.Z.f.Q.i.d.M., *Deutsches Instrument zur methodischen Leitlinien-Bewertung (DELBI) Fassung 2005/2006 + Domäne 8 (2008).* 2008: p. 13-47.
3. SIGN, *Scottish Intercollegiate Guidelines Network, Cochrane Risk of Bias Tool.*
4. Toosy, A.T., D.F. Mason, and D.H. Miller, *Optic neuritis.* Lancet Neurol, 2014. 13(1): p. 83-99.
5. Britze, J., G. Pihl-Jensen, and J.L. Frederiksen, *Retinal ganglion cell analysis in multiple sclerosis and optic neuritis: a systematic review and meta-analysis.* J Neurol, 2017. 264(9): p. 1837-1853.
6. Gal, R.L., S.S. Vedula, and R. Beck, *Corticosteroids for treating optic neuritis.* Cochrane Database Syst Rev, 2012(4): p. CD001430.
7. Optic Neuritis Study Group, O.N.S., *The clinical profile of optic neuritis. Experience of the Optic Neuritis Treatment Trial. Optic Neuritis Study Group.* Arch Ophthalmol, 1991. 109(12): p. 1673-8.
8. Sellebjerg, F., et al., *A randomized, controlled trial of oral high-dose methylprednisolone in acute optic neuritis.* Neurology, 1999. 52(7): p. 1479-84.
9. Wakakura, M., et al., *Multicenter clinical trial for evaluating methylprednisolone pulse treatment of idiopathic optic neuritis in Japan. Optic Neuritis Treatment Trial Multicenter Cooperative Research Group (ONMRG).* Jpn J Ophthalmol, 1999. 43(2): p. 133-8.
10. Beck, R.W., et al., *A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. The Optic Neuritis Study Group.* N Engl J Med, 1992. 326(9): p. 581-8.