S3 guideline "Rehabilitative therapy for arm paresis following a stroke" of DGNR – full version

1. Evidence classes, quality assessment of the evidence and recommended strengths

The aim of developing the S2e and S3 guidelines is to formulate evidence recommendations for practical clinical application based on a comprehensive, systematic search and critical assessment of the available evidence.

S2e guidelines are usually developed within one specialist company. S3 guidelines are developed by various specialist companies in accordance with the consensus method of the S2k guidelines (in addition to the systematic evidence-base). This guideline is an S3 guideline. This document gives a general outline of the method, which is based on the regulations of the Workgroup Scientific-Medical Specialist Companies (Arbeitsgemeinschaft wissenschaftlicher medizinischer Fachgesellschaften – AWMF) (https://www.awmf.org/leitlinien/awmf-regelwerk.html) and was explained in detail within the context of the DGNRL guideline development by Platz and Quintern in 2009, and by Platz in 2017. The aim is to enable the reader to trace the various assessment steps and classifications that form the foundation of the evidence-based recommendations. From evidence assessment to recommendation, the guideline development breaks down into the following work steps:

(I) *For individual sources (original widths, systematic reviews and meta analyses)*

    1. Methodical assessment (of the validity) of individual sources

    2. The evidence classification of individual sources (1a to 5 in accordance with "Oxford Centre for Evidence-based Medicine – Levels of Evidence", version of March 2009; http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march2009/

    3. Summary of findings, contents derived, and recommendations from the individual sources, and

(II) *Summary for all sources for one question (e.g. therapy method) (original widths, systematic reviews, and meta analyses)*

    4. Highest evidence class according to the Centre for Evidence-Based Medicine (CEBM) that was primarily used as evidence base for the treatment recommendation,

    5. Summary assessment of contents (quality and evidence) of the included sources in terms of the resulting trust in the assessment of the strength of the effect (of a therapy), and

    6. Classification of the derived recommendation for practical clinical application.

The evidence classes of the included studies / work were summarised for each question and/or target criterion. The highest evidence class according to the CEBM classification was stated, which was primarily used as evidence base for the treatment recommendation, i.e. from 1a (systematic review) to 5 (no evidence, expert opinion).

The *quality of the evidence* for a specific question or target parameter of a guideline is summarised and divided into four categories, similar to the "GRADE" system ("Grades of Recommendation, Assessment, Development and Evaluation, GRADE"; www.gradeworkinggroup.org) (Balshem et al., 2011):

- High quality – we are confident that the real effect is close to the estimated effect.
- Moderate quality – We have some trust in the estimated effect: the real effect is probably close to the estimated effect, but there is a possibility that it has relevant differences.
- Low quality – We have only limited trust in the estimated effect: the real effect could easily have relevant differences to the estimated effect.
- Very low quality – We have very little trust in the estimated effect: the real effect probably has relevant differences to the estimated effect.

The assessment of the "quality" in this respect (GRADE) aims to show the estimated level of stability of the data situation for a specific therapeutic option. "High quality" is prevalent, for instance, when meta analyses of numerous randomised, controlled studies with large number of patients and low variability (heterogeneity) of the results throughout the study give cause to assess the therapeutic effect as highly certain and it can be assumed that further studies will not greatly affect this appraisal. At the other end of the assessment spectrum are situations where no controlled studies have been carried out that give some certainty when assessing the therapeutic effect, for instance. A "very low quality" is assumed in this case.

The "quality" can only be assessed in this respect when the entire data situation from the clinical studies, systematic reviews and meta analyses is known and has been assessed. In this case, the final quality assessment is crucial for the clinical decision, and therefore the formulation of a recommendation. The quality assessment of the evidence in accordance with GRADE is based on a methodical outcome. In this guideline, the assessment was based on the therapeutic effects on the active arm functions (at damage or activity level) and/or the self-assessment of the usability of the paralysed arm, and not the potentially reported additional effects on basal competences in daily life, participation in the broadest sense, quality of life, recording of the acceptability of a therapy, or damage caused by therapy (side effects).

The *recommendation* for or against a certain intervention (corresponding target criterion is only determined in accordance with the above specification of the summarised quality of the evidence for a question.

According to the method, *recommendation grades* are then issued by the members of the guideline group as part of a formal consensus process. In addition to the GRADE criteria, additional criteria for the clinical assessment of applicability and transferability of the evidence are explicitly specified (Guyatt et al., 2006; Andrews et al., 2013):

- Assessment of the use versus risk
- Strength of the effect of the study findings and trust in their assessment
- Clinical relevance (suitability of the effectiveness measurements of the study with regard to supply, appropriateness of the controlled groups, and doses applied)
- Conformity of the values and preferences of affected persons
- Pathopsychological and clinical plausibilities
- Practicability of the guideline in actual therapeutic treatment (including resources requirements and consumption, etc., structure quality that does not yet exist)
- Ethical obligations (necessity to act)

The classification of the recommendations in this guideline complies with the AWMF regulations (AWMF 2012), the categories "Must" (A), "Should" (B), or "Could" (0) and/or the negative recommendations / refusal "Must not" (A-), "Should not" (B-) (see table 4).

Table 4 Classification of evidence, recommendation and consensus strength in guidelines as an expression of the extent of certainty / uncertainty of the knowledge base for the respective recommendations [according to Muche-Borowski and Kopp, 2015; and Platz, 2017]

Quality of the evidence	Underlying studies	Symbols
High	High-quality systematic work providing an overview (with or without meta-analysis) of randomised, controlled clinical studies (RCT)	1a
	Individual RCT with very low distortion risk and highly accurate estimated effect (narrow confidence interval)	1b
Moderate	High-quality systematic work providing an overview of cohort studies	2a
	Individual cohort studies with very low distortion risk and/or individual RCT with relevant distortion risk or little accurate estimated effect (broad confidence interval)	2b
Low	Case control studies	3
Very low	Case series, case reports	4

Recommendation grade	Formulation	
Strong recommendation	Must / must not	A / A-
Recommendation	Should / should not	B / B-
Open recommendation	To be considered	0

High quality of the evidence initially results in a strong recommendation, moderate quality to a recommendation, and low quality to an open recommendation. The additional criteria stated above for the clinical assessment of the applicability and transferability of the evidence can result in a deviation from this rule within the scope of the development of the recommendations: based on evidence, stronger or weaker recommendations could be formulated than would be the case if the sole basis were the quality of the evidence.

In terms of the recommendation, it also has to be remembered that they are effective within the context of a patient's individual rehabilitation targets. They apply to treatment situations where an improvement of the active arm function (at damage or activity level) and/or the self-assessment of the usability of the paralysed arm is the individual treatment target.

2. Occurrence / relevance

Arm paresis is one of the most common damages resulting from brain damage, such as a stroke. Hemiparesis (paralysis of one side of the body only) is one of the most significant predictors of long-term disability. The motor function of the affected arm can explain up to 50% of the variance (Mercier et al., 2001) in the functional autonomy of stroke patients. The extent of the damage to the arm function a few weeks after a stroke is associated with the strength of the disability after six months (Hankey et al., 2002; Meijer et al., 2003). This affects, for example, the difficulties and need for help with daily activities and the performance of social roles (Desrosiers et al., 2003). Arm paralysis also has a significant impact on whether patients will be able again to cope with daily life after a stroke.

3. Symptoms

The severity of arm paralysis after a stroke is not a normally distributed phenomenon. Arm paresis rather shows a bimodal distribution in numerous patients with either slight or severe limitations of arm activity (Nakayama et al., 1994; Wade et al., 1983). I.e., numerous patients are unable to functionally use their arm, and the same number of patients can perform numerous manual tasks, albeit in a clumsy manner.

Patients with severe arm paresis often cannot use their arm at all in daily life or only to a very limited extent. They have substantial problems with their voluntary motor function with significant limitations when moving or stabilising individual limb segments, to coordinate them individually and/or in groups, and to integrate dynamic movement aspects and holding activities. The symptoms of a disrupted voluntary motor function are often accompanied by symptoms from the "spastic" range with a pathological reaction of the muscles to stretching, increased resistance to passive movement, incorrect posture, and contraction of soft parts.

Patients with slight arm paresis have an almost full active movement scope and largely normal production of power and can use their arm accordingly for numerous daily activities. However, their movements are often still slow and they appear to be clinically clumsy. Daily life motor functions require complex and various sensomotoric skills, such as speed, fractioning of limb segment movements, gripping, and manual dexterity when manipulating objects, target orientation of movements or accurate eye-hand coordination, which are required in various combinations when performing daily tasks. The functional deficit of patients with slight arm paresis manifests in all of these areas and therefore in numerous daily tasks that require a certain extent of speed and accuracy.

Symptoms commonly associated with paralysis include somatosensory deficits that may affect surface quality (e.g. aesthesia, algesia, thermaesthesia, two-point discrimination) and/or proprioception (sense of position, pallaesthesia), and consecutively stereognosis. Various forms of sensitive paraesthesia and neurogenic pain syndromes are also frequently reported.

Arm activity in daily life can also be limited due to additional deficits which often occur after a stroke. After an insult of the left hemisphere, for instance, apraxia can often lead to bilateral restriction of the arm activity (Walker et al., 2004). The use of the contralesional arm in daily life may also be reduced due to neglect following damage to the right hemisphere (Vanbellingen et al., 2017), which can be improved again with neglect therapy (Nyffeler et al., 2019).

The treatment of impairments not caused by paresis, such as impaired sensitivity, apraxia or neglect, are not included in this guideline, but must be taken into consideration in connection with the treatment of impaired arm activity.

4. 6.28.6. Cerebrolysin

Cerebrolysin consists of neuropeptides with a low weight as well as free amino acids. It is extracted from pig's brain protein and has neuroprotective and neurotrophic properties. The drug is licensed in Austria for the treatment of strokes.

5. Randomised controlled studies

In an RCT with acute stroke patients, studies were performed to establish if Cerebrolysin promotes motor function recovery, particularly arm activities (Muresanu et al., 2016). 208
Patients were treated with i.v. Cerebrolysin (30 ml/day) or placebo (saline solution) and also received rehabilitative treatment from 24 to 72 hours after a stroke for a period of 21 days. Not only after treatment, but also during follow-up monitoring 90 days from the insult, the Verum group showed considerably stronger improvement. The median changes from baseline until 90 days after the insult for the ARAT (primary variable) were 30.7±19.9 (MW ±SD) [median 32.0 IQR 36.5] after administering Cerebrolysin and 15.9±16.8 [median 11.0 IQR 22.0] after administering the placebo.
The "global status", which was determined with 12 different scales, also showed a relevant superiority of the recovery in the Cerebrolysin group (Mann–Whitney estimator 0.62; 95% CI 0.58 – 0.65; P < 0.0001). The safety profile of Cerebrolysin was therefore comparable with the placebo treatment.

6. Recommendations

Cerebrolysin can be considered for (sub) acute stroke patients with relevant arm paresis when treatment targets are motor function recovery of the hand / arm function and overall functional recovery (evidence 1b, assessment of effects: moderate quality; recommendation grade 0; strong consensus).

If used, the drug should be started as quickly as possible (from 24 to 72 hours after the stroke) and, if tolerated, prescribed for 21 days, once a day, intravenously, in addition to rehabilitation (evidence 1b, assessment of effects: moderate quality; recommendation grade B; strong consensus). Specific information by the manufacturer must be taken into consideration.