PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Impact of Sight and Hearing Loss in Patients with Norrie Disease: Advantages of Dual Sensory Clinics in Patient Care
AUTHORS	Sowden, Jane Kros, Corné Sirimanna, Tony Pagarkar, Waheeda Oluonye, Ngozi Henderson, Robert

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. Lisbeth Tranebjaerg Institution and Country: Rigshospitalet, clinical genetics, United Kingdom of Great Britain and Northern Ireland Competing interests: None
REVIEW RETURNED	17-Jul-2020

GENERAL COMMENTS	Review-2020-bmjpo-2020-000781-170720 The burden of sight and hearing loss in patients with Norrie Disease: advantages of dual sensory clinics in patient care By Sowden JC et al The paper discusses the advantages of multidiscliplinary clinics for the medical care of patients with one genetic disease associated with dual sensory losses, namely Norrie Disease, in which condition there may also be additional impairmnets. The rarity of the disease associated with dual sensory impairment is without doubt strong arguments for organizing such clinics with all special medical and other qualifications of relevance for these patients. All conditions with deaf blindness will benefit from such assembly of medical care and the characteristics of each condition vary depending which of the sensory losses comes first and /or if additional abnormalities (seizures in Norrie) appear in addition. Multidiscliplinary care taking is known for deafblindness in other countries, like Sweden, and has contributed considerably to diagnose the specific condition and design habilitation and other treatment much more “targetly”than would otherwise happen. The paper might discuss the experiences which have been collected in Groningen, The Netherlands, where a clinic for CHARGE syndrome patients with the same dedicated multidiscliplinary focus is established. Such clinics also enhance the possibilities for quality research of many aspects of such rare syndromes. The paper focuses on paediatric patient but it is of equal importance to secure the transition in to adulthood and multidiscliplinary care in the adult age group. The paper is associated by a number of figures which unfortunately is with such a small font that they are impossible to read or evaluate in their content.

	Overall, the paper is well written and is fairly detailed , but also with some degree of redundancy in the sense of stressing the advantages of multidiscliplinary clinics. Some shortening would not decrease the importance of the messages in this paper. Some minor comments: On page 3, line30, the abbreviation PVD is not explained. On page 8, line 27 amniocentesis is mentioned as a prental genetic testing option, but today either early CVS or even PGD (pre implantation genetic diagnosis) would be the most relevant option. On page 10, line22, otoacoustic emissions are explained and this explanation should be more specific, namely that this OAE test can detect whether the outer hair cells are functioning (OHC) or not.

REVIEWER	Reviewer name: Dr. Elizabeth Hodges Institution and Country: United Kingdom of Great Britain and Northern Ireland Competing interests: None
REVIEW RETURNED	03-Aug-2020

GENERAL COMMENTS	I am an education specialist in dual sensory impairment and my review does not comment on medical aspects of the paper. Comments on the paper The provision of specialist clinics for dual sensory impaired children is well presented along with the potential benefits for parents and children, and is rooted in literature, with some reference to practice. There are important factors here, and Norrie Disease is a good example of the significance of dual sensory impairment, but that there are other significant conditions (some much more prevalent) such as Usher syndrome or CHARGE syndrome which could also benefit from this approach is not mentioned even though the discussion is widened to children with dual sensory impairment. While recognising the disabling features of ND the word 'burden' is a highly negative approach to the disease; the word 'impact' would be preferable in most places to recognise the significant effects of dual sensory impairment but to reduce the entirely negative connotations. Likewise, the phrase ‘cognitively intact’ is deficit based and could be replaced by ‘cognitively able’. Comments on topics The paper is about the special needs of children who have both vision and hearing impairment. It is therefore particularly disappointing that pg 11 line 7 suggests the involvement of specialist teachers of the hearing and visually impaired, but not specialist teachers of deafblind children. This is a profession accredited in the same way as HI and VI teachers and should certainly be recognised by the authors of the paper. It is particularly important that the impact of the two sensory impairments on each other is emphasised. This is the case in general in the paper, but two further important points could be linked. There is no mention for example of the effect of pupil dilating drops on the communication of deaf people, who may become unable then to lip read, or see signs or gestures. This is a very significant issue for many dual sensory impaired people and could be helpfully included at least on pg 15 line 22- where ‘discomfort, tiredness’ are mentioned but not the crucial factor that their communication may have become extremely difficult. As noted in the paper, not all ND patients may be completely blind

	and in terms of understanding dual sensory impairment this is particularly significant. Secondly in the paragraph on pg 12 beginning line 12, the increased reliance of blind children on hearing is mentioned- and the importance of early detection of cochlear dysfunction. Associated with these can be the benefits of amplification provided at hearing levels higher than those for sighted children. A mild loss can be much more significant than and require more intervention for a blind child. Line comments pg 8 line 21- many dual sensory impaired people continue to use signed language, although perhaps in tactile ways. This line should read 'sign language through visual means' or be omitted. It could include 'subtitles' or 'captions' if wishing to include another method which is clearly visual. pg 9 line 21 is very unclear as to whether the 'days missed at work' relate to parents of ND children or to older ND patients themselves. If it is both, this should be made clear. Pg 11 line 8 ‘Early intervention from developmental specialists is essential to guide parents in how to assist their child in all areas of development’ And line 19+ ‘As soon as blindness is detected in an infant they should be referred to a specialist developmental paediatrician with the expertise and resources to assess developmental issues’ Seem to say the same thing. Proofing errors; pg 6 line 27 'in ND these are hearing and vision in ND' (repeat of 'in ND'). Figure 2 box 5 Says ‘parent of an ND patient who’s hearing loss…’ Should be ‘parent of an ND patient whose hearing loss….’

VERSION 1 – AUTHOR RESPONSE

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Title: The Impact of Sight and Hearing Loss in Patients with Norrie Disease: Advantages of Dual Sensory Clinics in Patient Care

Authors: Jane C Sowden, Corné J Kros, Tony Sirimanna, Waheeda Pagarkar, Ngozi Oluonye, Robert H Henderson

Dear Prof. Choonara,

Thank you very much for providing us with detailed peer-review comments and giving us the opportunity to revise the above manuscript for publication in *BMJ Paediatrics*. We have now revised the manuscript according to the reviewers' recommendations (all edits saved as track changes) and have provided a detailed point-by-point response to each comment within this letter (please see below). Please note that alpage and line numbers quoted refer to those in the fully marked up version of the manuscript.

Though every effort has been made to meet the word limit for a review article, the manuscript is currently 3,454 words long. The increase in word count from the initial submission is as a result of including information about the multidisciplinary management of CHARGE disease and adding further detail to existing points where requested. In addition, the number of references cited in this manuscript has increased to 42. Though we have attempted to keep the reference number below the limit of 40, these additional references are to ensure that the additional information requested by reviewers has been thoroughly referenced.

We hope that this response addresses all the concerns raised by the reviewers and that you will now consider the manuscript suitable for publication.

We thank you again and look forward to hearing from you.

Yours sincerely,

Jane C Sowden

<u>Editors:</u>

1. Figure 3 should be two separate figures – one for diagnosis and one for management

> **Authors' response:** Thank you for this helpful suggestion, we have now divided Figure 3 into two separate figures (now labelled Figure 3 and Figure 4). Formatting changes have been made to Figure 4 to ensure it stands alone as a separate figure; information included in the figure has been re-arranged into five boxes, which read:
>
> > **"Annual monitoring by Ophthalmology**
> > Monitoring to ensure eyes are not painful, ocular symptoms are treated and adequate low vision educational support is given. Surgery may be considered in order to maintain light perception, if present.
> >
> > **Monitoring by Audiology every 6–12 months**
> > Monitoring for subclinical hearing loss or hearing loss progression, followed by timely intervention
> >
> > **Management by allied healthcare professionals**
> > Referral in infancy to child development team for developmental surveillance and care coordination. Professionals should include paediatricians, hearing, speech and language therapists, an educational team, social workers, support groups and psychologists
> >
> > **Monitoring in primary care, with referral to other specialists e.g. a neurologist, if required**

> **Ongoing habilitation, counselling and psychology support**”

Subsequent figures have been re-numbered. A caption has been included for Figure 4 (Page 21, lines 25–28):

> **“Figure 4. Management and monitoring of Norrie Disease patients**
>
> *Assessment by Audiology for subclinical hearing loss should also be performed as soon as possible after diagnosis, such that any losses can be managed quickly and appropriately. ND: Norrie Disease.”

The caption for Figure 3 has been amended (Page 21, lines 16–23):

> **“Figure 3. Norrie Disease Diagnostic Pathway**
>
> At present, no guidelines or set routes for diagnosis of ND are available – this pathway represents a typical route for patients as observed in day-to-day clinical practice and is informed by the authoring clinicians. Referral to specialist developmental services should be made as soon as the child is assessed to be blind. ND: Norrie Disease.”

2. Add a Box of Key Messages

Authors’ response: A box of key messages has been included (Page 3, line 1); this has been developed in accordance with the guidelines for a summary box required for original research articles detailed on the *BMJ Paediatrics* website. The key messages are as follows:

> “What is known about Norrie Disease (ND)?
>
> - ND is a rare condition of congenital or infantile blindness. In addition, the majority of ND patients experience progressive sensorineural hearing loss.
> - Dual sensory loss has a significant impact on ND patients and is associated with communication problems, additional educational needs and feelings of isolation.
> - Patients with ND require management and monitoring by a range of clinicians and specialists to help them reach their full potential.
>
> What does this review add?
>
> - It is proposed that Dual Sensory clinics would alleviate the impact of ND by providing coordinated care by clinical specialists familiar with the disease.
> - Care by clinicians aware of the needs of ND patients improves the patient experience and can ensure timely and appropriate intervention for hearing loss.
> - Clinics designed with the needs of sensory impaired children in mind, and with staff trained in effective communication skills, can alleviate the stress of appointments.”

Reviewer 1:

General comments: The paper discusses the advantages of multidisciplinary clinics for the medical care of patients with one genetic disease associated with dual sensory losses, namely Norrie Disease, in which condition there may also be additional impairments.

The rarity of the disease associated with dual sensory impairment is without doubt strong arguments for organizing such clinics with all special medical and other qualifications of relevance for these patients.

All conditions with deaf blindness will benefit from such assembly of medical care and the characteristics of each condition vary depending which of the sensory losses comes first and/or if additional abnormalities (seizures in Norrie) appear in addition.

> **Authors' response:** Thank you very much for your positive feedback on our manuscript. Responses to your additional comments can be found below; our revisions should help emphasise that a multidisciplinary approach can be of benefit in all conditions which feature deaf-blindness.

1. Multidisciplinary care taking is known for deaf-blindness in other countries, like Sweden, and has contributed considerably to diagnose the specific condition and design habilitation and other treatment much more "targetedly" than would otherwise happen. The paper might discuss the experiences which have been collected in Groningen, The Netherlands, where a clinic for CHARGE syndrome patients with the same dedicated multidisciplinary focus is established. Such clinics also enhance the possibilities for quality research of many aspects of such rare syndromes.

> **Authors' response:** Thank you for your suggestion of including experiences from multidisciplinary care of CHARGE syndrome. We have included additional information throughout the 'Advantages of Dual Sensory clinics' section to describe the use of multidisciplinary care in CHARGE syndrome in the Netherlands (Page 13, lines 25–28):
>
> > "In the Netherlands, the National Multidisciplinary CHARGE Clinic coordinates care for children and young adults with CHARGE syndrome and provides access to a wide range of clinicians, including a specialist communication and language development team; patients attend every one to two years."
>
> Unfortunately, we have been unable to find detailed information of the experiences from these clinics; we have instead referenced the experience of CHARGE syndrome patients in the UK who do not receive the same level of coordinated multidisciplinary care. These changes are included on Page 13, lines 15–18:
>
> > "In the UK, research into the experiences of patients with rare syndromes and sensory impairments has revealed that for complex diseases like CHARGE and Usher syndromes, care can be uncoordinated and spread across numerous clinics and hospitals."
>
> On Page 14, lines 2–4 (new text in bold):
>
> > "Many hospital environments are not designed with sensory impaired paediatric patients in mind; **this has been reported by both CHARGE and Usher syndrome patients in the UK**."
>
> At the start of this section, we introduce that CHARGE syndrome and Usher syndrome patients are known to benefit from a multidisciplinary approach (Page 12, lines 10–12):
>
> > "Beyond ND, multidisciplinary care is known to be beneficial for patients with a wide range of conditions which feature dual sensory loss, such as Usher syndrome and CHARGE syndrome."

Finally, we have expanded the Summary to address these conditions (Page 16, lines 5–9):

> "Coordinated multidisciplinary clinics specifically designed to cater to the needs of patients with sensory impairments would be of great benefit to patients with a wide range of complex rare diseases involving vision and hearing loss, including ND."

2. The paper focuses on paediatric patients, but it is of equal importance to secure the transition into adulthood and multidisciplinary care in the adult age group.

Authors' response: Thank you for highlighting this issue. We have included a short paragraph at the end of the 'Ongoing challenges' subsection to discuss the issue of the transition of care, and suggest that the coordination of patient care through a multidisciplinary clinic might help to secure this transition. This addition can be found on Page 15, lines 10–17:

> "The transition from paediatric to adult services is another challenge for patients with rare conditions, however, awareness of this issue is increasing. It has been suggested that transition planning should begin from 12–14 years of age, should cover a broad range of the patient's care needs and should involve a coordinating care provider. Dual Sensory and multidisciplinary clinics may help to facilitate this transition process, by ensuring that any changes to care are planned early and coordinated between teams to avoid disruption to care and distress to the patient."

3. The paper is associated by a number of figures which unfortunately is with such a small font that they are impossible to read or evaluate in their content.

Authors' response: Thank you for highlighting this. When creating the submission proof, the figures had been decreased in size and quality. High resolution figures have been uploaded for inclusion in the final version of the manuscript.

4. Overall, the paper is well written and is fairly detailed, but also with some degree of redundancy in the sense of stressing the advantages of multidisciplinary clinics. Some shortening would not decrease the importance of the messages in this paper.

Authors' response: Thank you for your feedback, we have reviewed the text and edited the 'Advantages of Dual Sensory Clinics' section (Page 12, line 6 to Page 15, line 17) to avoid redundancy.

5. On page 3, line 30, the abbreviation PVD is not explained.

Authors' response: Thank you for your feedback, the abbreviation of PVD had already been defined as "peripheral vascular disease" at the start of the sentence (Page 4, line 29).

6. On Page 8, line 27 amniocentesis is mentioned as a prenatal genetic testing option, but today either early CVS or even PGD (pre-implantation genetic diagnosis) would be the most relevant option.

Authors' response: Thank you for this helpful insight, we have inserted the following text to highlight these two additional testing methods, which have been appropriately cited within the text (Page 9, lines 21–27 [new text highlighted in bold below]):

> "Amniocentesis **or chorionic villus sampling with** genetic testing can be used to identify pathogenic *NDP* variants **and determine the sex of a fetus**, while early signs of ocular pathology can be detected using ultrasound. **Alternatively, pre-implantation genetic diagnosis can be used to screen embryos derived from *in vitro* fertilisation to reduce the risk that a child inherits a pathogenic copy of *NDP*.**"

7. On Page 10, line 22, otoacoustic emissions are explained and this explanation should be more specific, namely that this OAE test can detect whether the outer hair cells are functioning (OHC) or not.

   Authors' response: Thank you for your feedback, we have altered the wording of this sentence to specify that OAE testing can detect the functioning of the OHCs (see Page 11, lines 22–26 [new text highlighted in bold below]):

   > "Early referral to audiology **specialists** is recommended to allow for monitoring with appropriate behavioural or objective tests such as otoacoustic emissions (sounds generated **by the outer hair cells** within the inner ear) for the early detection of cochlear dysfunction."

Reviewer 2:

General comments: The provision of specialist clinics for dual sensory impaired children is well presented along with the potential benefits for parents and children, and is rooted in literature, with some reference to practice.

Authors' response: We thank you for your thorough review of this manuscript. Please see below for details on how we have addressed each of your comments.

1. There are important factors here, and Norrie Disease is a good example of the significance of dual sensory impairment, but that there are other significant conditions (some much more prevalent) such as Usher syndrome or CHARGE syndrome which could also benefit from this approach is not mentioned even though the discussion is widened to children with dual sensory impairment.

   Authors' response: Thank you for this helpful suggestion. We have included additional information throughout the 'Advantages of Dual Sensory clinics' section to describe the use of multidisciplinary care in CHARGE syndrome and Usher syndrome.

   At the start of this section, we introduce that CHARGE syndrome and Usher syndrome patients are known to benefit from a multidisciplinary approach (Page 12, lines 10–12):

   > "Beyond ND, multidisciplinary care is known to be beneficial for patients with a wide range of conditions which feature dual sensory loss, such as Usher syndrome and CHARGE syndrome."

   Page 13, lines 25–28:

   > "In the Netherlands, the National Multidisciplinary CHARGE Clinic coordinates care for children and young adults with CHARGE syndrome and provides access to a wide range of clinicians, including a specialist communication and language development team; patients attend every one to two years."

   Page 13, lines 15-18:

   > "In the UK, research into the experiences of patients with rare syndromes and sensory impairments has revealed that for complex diseases like CHARGE and Usher syndromes, care can be uncoordinated and spread across numerous clinics and hospitals."

   Page 14, lines 2–4 (new text in bold):

   > "Many hospital environments are not designed with sensory impaired paediatric patients in mind; **this has been reported by both CHARGE and Usher syndrome patients in the UK**."

Finally, we have expanded the Summary to address these conditions (Page 16, lines 5–9):

> "Coordinated multidisciplinary clinics specifically designed to cater to the needs of patients with sensory impairments would be of great benefit to patients with a wide range of complex rare disease involving vision and hearing loss, including ND."

2. While recognising the disabling features of ND the word 'burden' is a highly negative approach to the disease; the word 'impact' would be preferable in most places to recognise the significant effects of dual sensory impairment but to reduce the entirely negative connotations. Likewise, the phrase 'cognitively intact' is deficit based and could be replaced by 'cognitively able'.

Authors' response: Thank you for your feedback and suggestions, we have reviewed the text, replacing 'burden' with 'impact; and 'cognitively intact' with 'cognitively able' where appropriate throughout the manuscript.

3. The paper is about the special needs of children who have both vision and hearing impairment. It is therefore particularly disappointing that Page 11, line 7 suggests the involvement of specialist teachers of the hearing and visually impaired, but not specialist teachers of deaf-blind children. This is a profession accredited in the same way as HI and VI teachers and should certainly be recognised by the authors of the paper.

Authors' response: Thank you for this helpful suggestion and please accept our apologies for this omission, we have now adjusted this sentence to ensure that we also acknowledge the involvement of teachers for deaf-blind children too (Page 10, line 5):

> "Management of patients with ND requires input from a team of specialists and allied healthcare professionals, including paediatricians, hearing, speech and language therapists, an education team (including qualified teachers for the hearing impaired, the visually impaired and the deaf-blind), social workers, support groups, psychologists and developmental specialists."

4. It is particularly important that the impact of the two sensory impairments on each other is emphasised. This is the case in general in the paper, but two further important points could be linked. There is no mention for example of the effect of pupil dilating drops on the communication of deaf people, who may become unable then to lip read, or see signs or gestures. This is a very significant issue for many dual sensory impaired people and could be helpfully included at least on Page 15, line 22- where 'discomfort, tiredness' are mentioned but not the crucial factor that their communication may have become extremely difficult. As noted in the paper, not all ND patients may be completely blind and in terms of understanding dual sensory impairment this is particularly significant.

Authors' response: Thank you for your feedback. We have included an additional sentence here to highlight the impact of dilating drops on partially sighted patients (Page 15, lines 1–3):

> "Further challenges may be experienced by the minority of ND patients who have some visual function, as the dilating drops may further compromise their access to visual cues for communication."

However, as visual function greater that light perception has been reported in an extremely small number of ND cases (and most often in case studies of surgical interventions in which the long-term impact of the intervention is not known), we have not greatly emphasised this point.

5. Secondly in the paragraph on Page 12, at the beginning of line 12, the increased reliance of blind children on hearing is mentioned - and the importance of early detection of cochlear dysfunction. Associated with these can be the benefits of amplification provided at hearing levels higher than those for sighted children. A mild loss can be much more significant than and require more intervention for a blind child.

Authors' response: Thank you for this helpful insight, we have revised the text to highlight the importance of providing timely hearing interventions, particularly among completely blind children (Page 7, lines 15–17 and Page 10, line 26 to Page 11, line 2 [the new text in highlighted in bold below]):

> "Additionally, this amplification may be required at a higher level of hearing than in a sighted person, as mild hearing losses can have a more substantial impact in blind patients." [Page 7, lines 15–17]
>
> "Hearing aids are a common intervention for ND patients, and treating audiology professionals should have a good knowledge of the range of hearing aids available (including those not accessible though the patient's health service or medical insurance) in order to suggest the most appropriate devices. **In particular, clinicians should be aware of the benefits of intervention for even mild hearing losses in blind patients**." [Page 10, line 26 to Page 11, line 2]

6. Page 8, line 21 – Many dual sensory impaired people continue to use signed language, although perhaps in tactile ways. This line should read 'sign language through visual means' or be omitted. It could include 'subtitles' or 'captions' if wishing to include another method which is clearly visual.

Authors' response: Thank you for your suggestion, we have changed the wording here to 'sign language through visual means' (Page 7, line 22).

7. Page 9, line 21 is very unclear as to whether the 'days missed at work' relate to parents of ND children or to older ND patients themselves. If it is both, this should be made clear.

Authors' response: Thank you for highlighting this ambiguous point, we have revised this sentence to clarify that the reference to days missed at work relates to parents of ND patients only (Page 8, lines 17–19):

> "Further costs may be incurred for childcare, or loss of earnings may result from parents of patients with ND having to miss days from work."

8. Page 11, line 8: 'Early intervention from developmental specialists is essential to guide parents in how to assist their child in all areas of development', and line 19+ 'As soon as blindness is detected in an infant they should be referred to a specialist developmental paediatrician with the expertise and resources to assess developmental issues' seem to say the same thing.

Authors' response: Thank you for your feedback, we feel it is necessary to highlight the importance of the developmental team both in identifying developmental issues as they arise and engaging with the parents, from day one if possible, to prepare them for the challenges they and their child will face. We have revised the text for clarity in order to differentiate these as separate points:

> "Management of patients with ND requires input from a team of specialists and allied healthcare professionals, including hearing and speech therapists, an education team (including qualified teachers for the hearing impaired, visually impaired and the deaf-

> blind), social workers, support groups, psychologists **and developmental specialists**.” [Page 10, lines 2–6, new text highlighted in bold]
>
> “As soon as blindness is detected in an infant they should be referred to a specialist developmental paediatrician with the expertise and resources to assess developmental issues **as they arise**. Work with **a team of developmental specialists** should begin as early as possible to minimise the impact of visual impairment on the patient; **the intervention, support and advice of developmental specialists is essential to guide parents in how to assist their child in all areas of development**.” [Page 10, lines 18–24, new text highlighted in bold]

9. Page 6, line 27: 'in ND these are hearing and vision in ND' (repeat of 'in ND'), and Figure 2 box 5 Says ‘parent of an ND patient who’s hearing loss…’ Should be ‘parent of an ND patient whose hearing loss….’

Authors’ response: Thank you for identifying these proofing errors, they have been corrected according to your suggestions.